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SYNTEX agribusiness inc

NUTRITION AND CHEMICAL DIVISION

ENVIRONMENTAL PROJECTS DEPARTMENT

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April 21, 1988

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SUPERFUND RECORDS

Rowena Michaels, Director
Office of Public Affairs
U.S. Environmental Protection Agency
Region VII
726 Minnesota Avenue
Kansas City, Kansas 66101

Dear Ms. Michaels:

In response to the United States Environmental Protection Agency's request for comments, Syntex Agribusiness, Inc. respectfully submits the enclosed comments and related documentation concerning the "Proposed Plan for Final Management of Dioxin Contaminated Soil and Equipment, Syntex, Verona" dated March, 1988.

Sincerely,

SYNTEX AGRIBUSINESS, INC.

Ray K. Forrester

Ray K. Forrester
Manager, Environmental Projects

9641X/0150F

Enclosure

MAILING ADDRESS: P.O. BOX 1246, SPRINGFIELD, MO 65801 • (417) 866-4050 ALTERNATE NO. (417) 866-7291
SHIPPING ADDRESS: 2460 WEST BENNETT, SPRINGFIELD, MO 65807

COMMENTS OF SYNTEX AGRIBUSINESS, INC.
ON THE "PROPOSED PLAN FOR FINAL MANAGEMENT
OF DIOXIN CONTAMINATED SOIL AND EQUIPMENT
SYNTEX, VERONA"

Syntex Agribusiness, Inc. ("Syntex") presents its comments on the March, 1988 Proposed Plan for Final Management of Dioxin Contaminated Soil and Equipment at the Syntex facility in Verona, Missouri ("Verona Proposed Plan") prepared by the U.S. Environmental Protection Agency ("EPA"). Syntex requests that EPA consider and incorporate these comments into its Record of Decision for this site.

Syntex has previously provided additional relevant information and comments to EPA regarding the following EPA documents:

Responsiveness Summary

1. September 4, 1986 on the Draft Minker/Stout/Romaine Creek Feasibility Study ("Draft M/S/RC FS");

2. March 26, 1987 on the Draft Times Beach Remedial Investigation/Feasibility Study ("Draft Times Beach RIFS");

3. September 18, 1987 on the Proposed Plan for Interim Management of Dioxin-Contaminated Sediment, Romaine Creek Portion of the Minker/Stout/Romaine Creek Site (August 1987); on the Public Comment Draft Operable Unit Feasibility Study, Romaine Creek Portion of the Minker/Stout/Romaine Creek Site (July 8, 1987); on the Proposed Plan for Interim Management of Dioxin-Contaminated Sediment, Stout Portion of the Minker/Stout/Romaine Creek Site (August, 1987); and on the Public Comment Draft Operable Unit Feasibility Study, Stout Portion of the Minker/Stout/Romaine Creek Site (July 8, 1987)("M/S/RC OUFS"); and

4. March 17, 1988 on the Public Comment Draft proposed Plan for Final Management of Dioxin-Contaminated Soil and Final Disposition of Structures and Debris at Times Beach, Missouri and the Minker/Stout/Romaine Creek Site, Missouri ("Times Beach Proposed Plan").

All of these earlier comments are hereby incorporated by reference into today's comments. Syntex requests that EPA also consider and incorporate these comments into its Record of Decision for this site.

On February 22, 1988, Syntex also submitted comments to the Agency for Toxic Substances and Disease Registry (ATSDR) regarding the toxicology profile for dioxin ("Syntex ATSDR Comments"). These comments are attached and incorporated by reference into today's comments. Syntex requests that EPA also consider the Syntex ATSDR Comments and incorporate them in its Record of Decision for this site.

Finally, Syntex has submitted to EPA Remedial Alternative Reports for the Verona facility dated October 4, 1987; September 30, 1987; and March 3, 1988. These three Remedial Alternative Reports also are hereby incorporated by reference into today's comments. Syntex requests that EPA consider and incorporate these Reports into its Record of Decision for this site.

INTRODUCTION

Syntex has collected extensive information regarding its Verona facility as described in the Revised Remedial Alternatives Report ("Remedial Report") submitted to EPA on March 3, 1988. The Remedial Report demonstrates that public health and the environment are not being endangered at the site. All of the remedial alternatives discussed in the Remedial Report, including the No Action Alternative, assure protection of human health and the environment.

1.

The Remedial Report uses a 20 ppb level of concern previously suggested by EPA for tetrachlorodibenzo-p-dioxin ("TCDD") at nonresidential sites. A much higher level of concern, however, could safely be used at the site. As discussed in detail in Syntex's previous comments incorporated by reference today, this level of concern significantly overestimates the potential risk presented by the TCDD contamination at the site. Those prior comments examine flaws in the assumptions underlying the levels of concern, focusing especially on the values adopted for the quantity of soil ingested by children, and for the bioavailability of TCDD that is bound to soil. EPA also has not incorporated important scientific advances into its methodology of estimating cancer risk, and as a result embraces a mathematical approach that yields conclusions at odds with the rest of the scientific community. This is especially true with respect to EPA's use of the linearized multistage low dose extrapolation model that fails to distinguish between initiation and promotion as the mechanism of carcinogenesis. These issues are discussed in more detail below.

2.

In spite of the fact that the 20 ppb level of concern for TCDD is unnecessarily restrictive, the Remedial Report proposes remedial actions based on this level of concern. These remedial actions, therefore, are extremely conservative and no additional actions should be required. Discrepancies between the Remedial Report and the Proposed Plan also are discussed in more detail below.

A. HEALTH ISSUES

In its comments on the Draft Times Beach RIFS, the M/S/RC OUFS, and the Times Beach Proposed Plan, Syntex presented an extensive critique of EPA's methodology for assessing cancer risk due to exposure to TCDD contaminated soils, and the conclusions the Agency has drawn from the application of its risk assessment methodology. As discussed in those comments, EPA has overestimated both the soil ingestion value and the value for oral bioavailability of TCDD in Missouri soil. EPA also has made a number of other overly conservative and unrealistic assumptions in determining TCDD levels of concern, such as the extent of surface contamination, duration of dermal exposure, and the use of the linear low-dose extrapolation model that assumes an incorrect mechanism of carcinogenesis. By making scientifically justifiable corrections to a few of these erroneous assumptions, Syntex arrives at more reasonable and supportable levels of concern that are more than amply protective of human health and the environment.

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Same as TB

same as TB

Syntex iterates its criticism, raised previously in its comments on the Times Beach Proposed Plan, that EPA's methodology for assessing TCDD cancer risk is at odds with those of other regulatory agencies, both in the United States and abroad. The Ontario Ministry of Health, the State Institute of Health of the Netherlands, the Federal Environmental Agency of the Federal Republic of Germany, and the U.S. Food and Drug Administration all have rejected the use of the linearized multistage low dose extrapolation model. These agencies have concluded that TCDD is not a cancer initiator, and that the risk associated with TCDD would be better approximated by the application of a safety factor approach. EPA's risk assessment is more conservative by many orders of magnitude than that of any of the aforementioned regulatory agencies. To the extent that EPA purports to justify various elements of its proposed remediation program on health-based grounds, flaws in EPA's methodology for assessing TCDD risk make these elements unnecessarily restrictive.

On April 8, 1988 Dr. William Farland of the U.S. Environmental Protection Agency announced to a symposium sponsored by the California Academy of Sciences, the U.S. Environmental Protection Agency, and the Northern California Chapter of the Society for Risk Analysis that EPA headquarters was reconsidering its cancer risk assessment and was proposing to adopt a less restrictive cancer risk assessment. For the reasons described above, Syntex supports this reconsideration and urges EPA to adopt a cancer risk assessment based on the best scientific information and judgment available.

Syntex also contests EPA's conclusions in the Verona Proposed Plan that dioxin causes altered liver function and lipid metabolism, as well as neurotoxicity. It may be true that dioxin is highly toxic in certain animal species, with an LD_{50} in guinea pigs of 0.6 micrograms per kilogram. However, its toxicity to humans, apart from chloracne, has not been demonstrated. While dioxin may have been shown to cause chloracne in humans, it has not been shown to cause thymic atrophy, wasting syndrome, or any other adverse health effects. No human deaths have been determined to have resulted from dioxin exposure.

Because dioxin exists almost exclusively as an impurity in herbicides and bactericides, human exposure to dioxin is necessarily accompanied by exposure to the final product as well as other chemicals that may also be present. Consequently, ATSDR's Draft Toxicological Profile of Dioxin (ATSDR, 1987) indicates that impaired liver function is most likely attributable to exposure to these other chemicals, and not to dioxin. Other scientists have arrived at similar conclusions. For example, Jones and Chelsky (1985) reviewed the alleged link between porphyria and dioxin and concluded that dioxin was not the causative agent, and that other chemicals that were present were responsible for the porphyria.

There is ~~little~~ evidence that dioxin causes neurological effects in humans. In the Missouri Pilot Study, no neurological deficits were reported (Hoffman et al., 1986; Stehr et al., 1986; Webb et al. 1987). The most recent update of the Ranch Hand study indicated that dioxin did not cause neurological effects (Lathrop et al., 1987). Reportings of neurological effects come from industrial-type exposures, which are confounded by the concomitant exposures to high concentrations of other chemicals. In properly conducted epidemiological studies in humans, these neurological effects have not been causally determined to have resulted from dioxin.

The only documented effect of dioxin in humans is chloracne (AMA, 1984; ATSDR, 1987). Chloracne is considered the most sensitive indicator of toxicity in humans exposed to dioxin (Suskind, 1985). In the absence of chloracne, adverse health effects are not expected.

TB

The Verona Proposed Plan is misleading in its comparison of the carcinogenic potency of dioxin with that of bis-chloromethyl ether and vinyl chloride, two known human carcinogens. Despite the large amount of epidemiological data on dioxin, it has not been demonstrated that dioxin causes cancer in humans (IARC, 1982; AMA, 1984; Lathrop et al., 1987.

B. REMEDIATION ISSUES

The Verona Proposed Plan sets forth various proposals for remediating equipment and soil at the Verona site. Syntex supports the measures proposed for remediating the equipment and the comments herein are, therefore, limited to the six alternative proposals for soil remediation. Syntex' comments are divided into (1) general comments applicable to the proposed plan and remedial measures as a whole, and (2) specific comments as to the various remedial measures and subsites discussed in the Proposed Plan.

1. General Comments

Syntex fully supports EPA's approach of subdividing the site into separate subsites and tailoring the remediation measures to the specific characteristics of each subsite. It is Syntex' view, however, that the Proposed Remedy is overly conservative and that implementation of the Proposed Remedy is not necessary to protect public health and the environment. Other proposed alternatives are less costly, more readily implemented, of equal or greater long-term effectiveness, and fully protective of human health and the environment.

TB

As discussed in more detail above, the 20 ppb action level proposed in the Plan is extremely conservative. Concentrations of dioxin higher than 20 ppb in soil at nonresidential sites do not create appreciable health risks. Accordingly, an "action level" of 20 ppb for soil at this site is factually, scientifically, and legally unsupportable.

Moreover, the Proposed Plan does not make clear that the CDC and ATSDR advisories from which EPA derived the proposed 20 ppb action level for the Verona site were premised upon average dioxin concentrations. As a result, it would be a misapplication of the CDC/ATSDR guidance to require excavation of subsites where the average surface concentration of dioxin is less than 20 ppb. For example, the average surface contamination in the Burn Area and Irrigation Area subsites is 6.5 ppb and 4.0 ppb, respectively. Under a proper application of the CDC/ATSDR guidance, these subsites would require no remediation unless verification sampling showed that these values were not accurate reflections of the surface concentration of dioxin. If the values do accurately reflect surface concentration of dioxin, the Proposed Plan's excavation and off-site incineration of an estimated 60 cubic yards of soil from those two subsites at an estimated cost of $1.2 million would be unnecessary. Syntex understands that it is EPA's intention to require verification sampling of the top two inches in these locations and to require excavation only if the <u>average</u> surface concentration of dioxin is more than 20 ppb.

Syntex concurs with the statements in the Proposed Plan that soil containing average surface concentrations of 20 ppb or less of dioxin at nonresidential sites poses a minimal risk. Syntex also agrees with EPA's view that dioxin is virtually water-insoluble and binds tightly to soil, so that its presence in soil at levels of 20 ppb or less does not create any significant risk of groundwater contamination or entry into the food chain by uptake in plants.

The only conceivable (but probably insignificant) health or environmental risk from the presence of dioxin at levels below 20 ppb is the possible erosion of the soil into the Spring River, which theoretically could result in bio- accumulation in fish to levels in excess of those recommended for fish consumed by humans. In this connection, it should be emphasized that extensive sediment and fish sampling to date has failed to demonstrate that such erosion and bio-accumulation have occurred as a result of the current conditions at the site. In view of the foregoing, EPA is correct in concluding any remedial alternative (other than "no action" alternative or erosion prevention measures) is unjustifiable where average surface contamination is 20 ppb or less.

2. <u>Deep Tillage/Soil Inversion</u>

Notwithstanding EPA's current position that remediation of any areas with average dioxin concentrations below 20 ppb is scientifically <u>unjustifiable</u>, should EPA subsequently determine that some remedial action is desirable, then consideration should be given to the deep tillage/soil inversion technique (described in Appendix 22 to the <u>Verona Plan Sampling and Analysis Plan "Revised Remedial Alternatives Report" (Second Revision dated March 3, 1988</u>) incorporated by reference into these comments (hereinafter referred to as the "Second Revised Verona Report"). Soil inversion is a more appropriate and cost-effective remedial technique than excavation and off-site incineration of soil from areas having average surface contamination of less than 20 ppb.

3. Excavation

For the reasons stated above, it is Syntex' position that no excavation whatsoever is required for subsites containing average surface contamination of less than 20 ppb.

X The Proposed Plan indicates (at pp. 38-39), somewhat ambiguously, that areas having concentrations greater than 20 ppb "will be excavated up to a four-foot depth or bedrock." The ROD or final workplans for any excavation required under the remedial alternative to be implemented at the Verona site should make clear that excavation beyond the four-foot depth or bedrock (whichever is reached first) is not required. It should also be made clear that all excavation will be performed in stages or lifts (as described in the Second Revised Verona Report) and that, depending upon the analytical results of samples taken after each such stage, excavation to a depth of four feet or to bedrock may not be required.

X The Proposed Plan contemplates that additional sampling will be performed to determine precisely which areas of the site must be excavated. However, the Proposed Plan also states that excavation will be performed by using a backhoe. While the use of a backhoe is an effective and reasonably cost-efficient means of excavating small areas, other types of equipment, such as earth movers or graders, are equally effective but far more cost-efficient for excavating large areas. The ROD and/or final workplans for the Verona site should permit the excavation to be performed by backhoe or such other excavation equipment as will be most efficient cost-effective depending upon the size of the areas that are actually excavated.

4. Sampling Procedure.

X The Proposed Plan contemplates that sampling will be conducted in accordance with the "procedure utilized during the cleanup of other Missouri dioxin sites." The use of that sampling procedure unnecessarily inflates the remediation costs for the Verona site. Such sampling can be accomplished at a lower cost but with the same 95% confidence level by using the sampling protocol described in detail in Appendix 15 of the Second Revised Verona Report. This alternative sampling protocol should be incorporated in the final remedial action. At the very least, EPA should conduct (or permit Syntex to conduct) parallel sampling using both sampling protocols and, if the results of the parallel sampling are substantially similar, then complete all remaining sampling using the more cost-efficient protocol.

5. Incineration and Delisting.

MIS issue - impediments

The Proposed Plan contains numerous references to the possibility that soil excavated from the Verona site may be transported to and thermally processed in the Mobile Incinerator ("MIS") at the Denney Farm site. Syntex agrees that thermal processing in the MIS is capable of decontaminating such soil. However, at present there remain several impediments to implementing the Proposed Remedy: (1) the Denneys have not agreed to grant an easement to permit soil excavated from the Verona site to be transported to the Denney Farm; (2) EPA and Syntex have been unable to negotiate an agreement for such soil to be incinerated at the MIS for a reasonable cost; and (3) delisting criteria for the residues to be generated from the incineration of such soil have not yet been established by EPA. Syntex is, therefore, constrained to emphasize that incineration of the Verona materials at the Denney Farm site cannot occur unless and until these impediments are removed.

MIS ash delisting issues

In its discussion of the merits of the Proposed Remedy, EPA points to the fact that operation of the MIS has demonstrated that the residues from the treatment of dioxin-contaminated materials can be successfully delisted. However, the major contributing factor in this success story was the relatively reasonable delisting standards applicable to the MIS by virtue of the delisting exclusion promulgated in 1985. In contrast, EPA has proposed for the Verona soil (and other Syntex materials) excessively stringent, overly conservative standards that are far more demanding than those previously applicable to MIS operations. See 52 Fed. Reg. 33439 (Sept. 3, 1987). These proposed new criteria are based upon the application of a mathematical environmental fate model that improperly fails to take into consideration the actual disposal method and characteristics of the waste. Syntex understands, however, that EPA Headquarters has recently decided that excavated Verona soils would be delisted pursuant to the more reasonable 1985 delisting standards. Syntex has not received written confirmation of this decision. Without approved delisting criteria, it is impossible to determine whether the residues can in fact be delisted and, hence, disposed of as non-hazardous waste.

It is Syntex' position that the 1985 standards are amply protective of human health and the environment, and are sufficiently commensurate with dioxin levels of concern currently recommended by the regulatory agencies to warrant their continued application to MIS residues generated from the incineration of the soil excavated from the Verona site. There is no logical rationale for imposing criteria for delisting the MIS' residues to be generated from incinerating Verona soil different from the criteria for delisting such residues in 1985. Nor is there any logical reason for requiring treatment residues to attain dioxin levels that are many orders of magnitude below the current, ultra-conservative action levels for remediation of dioxin contaminated soil. Syntex believes that these proposed new criteria are scientifically, legally or factually unjustifiable and questions whether the residues from the MIS can satisfy them.

MIS destroy TCDD to "ND" levels

It should be noted that the Proposed Plan contains several references to the fact that the MIS has successfully destroyed dioxin in soil to "undetectable levels." Syntex believes this to be an overstatement of the facts. The current analytical detection levels for dioxin are in fact much lower than the levels of dioxin which EPA, in the 1985 delisting rulemaking, estimated to be present in MIS residues. Moreover, since the 1985 delisting criteria require only that the MIS be "operating properly" and do not require ongoing testing for dioxin in the residues (and Syntex is unaware that any such testing has been performed), there does not appear to be any factual basis for the Proposed Plan's claims as to the MIS' dioxin-destruction capabilities. In addition, the Proposed Plan erroneously claims (at page 25) that the MIS' "destruction and removal efficiency [DRE] is high enough to allow delisting of the contaminated soil following treatment." DRE, however, is a very specific technical term (related to exhaust gas from the MIS) that has nothing whatever to do with the delistability of the MIS' ash or residues.

Excav. soil & store onsite ?

X Syntex opposes the suggestion at page 26 of the Proposed Plan that contaminated soil be excavated and stored onsite "in the event that excavated soils are not incinerated at the Denney Farm site." Given that the dioxin contamination in the current conditions at the site poses no substantial threat to the environment or public health, there is no justification for requiring any excavation at the Verona site prior to assuring that the soil can and will be thermally processed at a reasonable cost and without producing residues which, like the soil itself, are ineligible for land disposal. In fact, the attendant double-handling of this material, and its above-ground storage, may actually increase the potential for human exposure to dioxin. Accordingly, the selection of the final remedial action for the site should provide that subsites requiring excavation be maintained in their current condition until suitable off-site treatment can be and is secured.

6. <u>Groundwater</u>

The Proposed Plan contemplates a groundwater monitoring program and states (at page 40) that "[i]f data generated from this monitoring shows contamination of the groundwater at levels of concern, remediation of the groundwater will be conducted through a second operable unit." The only groundwater data presented in the Proposed Plan are "maximum concentrations" for the years 1982 through 1986. Thus, there appears the danger that "maximum" concentrations will be mistakenly relied upon as triggering any future groundwater remediation. As with soil contamination, it is the <u>average</u> (and not the maximum) contamination detected in groundwater samples which truly indicates the groundwater quality and is determinative of whether the groundwater at the site meets applicable water quality standards.

With regard to groundwater contamination, it should be noted that the average groundwater concentrations (based upon existing data) for all the contaminants listed at pp. 7-8 of the Proposed Plan do not exceed the levels established for the protection of aquatic life under the Missouri water quality standards. Moreover, even the "maximum" concentrations, for the most part, do not exceed those standards. Consequently, it is Syntex' understanding that no groundwater remediation will be required at the site unless the results of the future groundwater monitoring are significantly different from the past results. This point should also be clarified in the final remedial action plan.

COMMENTS OF SYNTEX AGRIBUSINESS, INC.

on the

DRAFT TOXICOLOGICAL PROFLE FOR
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

by

THE AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

February 22, 1988

SUMMARY OF COMMENTS ON THE
DRAFT TOXICOLOGICAL PROFILE FOR
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

This document and its associated attachments constitute the comments of Syntex Agribusiness, Inc. (Syntex) on the November 1987 Draft Toxicological Profile for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (Draft Profile). The attachments consist of a bibliography of the references cited in the comments and copies of those supporting references cited by Syntex that are not cited by ATSDR in the Draft Profile and that may be difficult for ATSDR to obtain. These additional references are helpful in supporting or refining many of the conclusions reached in the Draft Profile.

We would first like to commend the Agency for Toxic Substances and Disease Registry (ATSDR) for producing a readible and informative draft on a very technical subject. The Draft Profile consists of an impressive compilation and summary of the health effects data that have been generated concerning 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (2,3,7,8-TCDD) from years of very intensive study and experimentation. The Draft Profile also objectively draws important conclusions from the accumulated data concerning the human health effects of 2,3,7,8-TCDD. There is substantially more information on the toxicity of 2,3,7,8-TCDD than for many other hazardous substances. The Draft Profile has done a good job in presenting this vast array of data in a manner that can be understood by the general public. This is an important accomplishment because a significant purpose of the Toxicological Profiles is to convey health effects information to the public as well as to the scientific community and governmental health officials.

However, we suggest that ATSDR expand the current scope of the Draft Profile by developing a toxicity standard and exposure levels for 2,3,7,8-TCDD. Many of our comments offer suggestions and references for the development of these health-based levels. We also offer comments on the narrative descriptions of the human health effects of 2,3,7,8-TCDD and provide references that support the conclusion in the Draft Profile that chloracne is the only demonstrated adverse human health effect resulting from exposure to 2,3,7,8-TCDD.

Our comments are organized to correspond to sections and subsections in the Draft Profile. Our comments are preceded by this summary, which is designed to highlight some of our major suggestions.

Introduction

We believe that a central focus of the Draft Profile should be the development of health-based standards for 2,3,7,8-TCDD. To develop these standards, ATSDR should first calculate a toxicity value (the level presenting minimal risks of adverse human health effects) for 2,3,7,8-TCDD as well as undertake exposure assessments for selected sources of potential human contact with 2,3,7,8-TCDD. The toxicity value and exposure assessments would then be used to calculate acceptable human exposure levels for 2,3,7,8-TCDD in different media.

The Draft Profile should not endorse the existing toxicity levels and acceptable exposure levels developed by the U.S. Environmental Protection Agency (EPA) or Kimbrough et al. of the Centers for Disease Control (CDC). These values are based upon assumptions that are no longer accepted by the general scientific community and, in fact, are being critically re-evaluated by EPA and CDC themselves. We submit that ATSDR, in calculating the toxicity value for 2,3,7,8-TCDD, should use a No Observed Adverse Effect Level (NOAEL) rather than the linearized multistage model employed by EPA and CDC.

The Draft Profile should explain the bases and correct application of the minimal risk levels developed by ATSDR and appearing on Figures 1.1 and 2.3. It is very difficult to assess the accuracy or application of these levels in the absence of an explanation as to their derivation and purpose. It appears that these minimal risk levels may have been developed using a NOAEL and that they may constitute 2,3,7,8-TCDD toxicity standards. If this is correct, we strongly endorse the approach taken by ATSDR and offer suggestions and additional references in the comments that follow to refine the calculated risk levels.

We also strongly support the conclusion in the Draft Profile that chloracne is the only demonstrated human health effect resulting from exposure to 2,3,7,8-TCDD. In addition, we would emphasize that chloracne is the most sensitive indicator of 2,3,7,8-TCDD toxicity in humans. We also support related conclusions in the Draft Profile that other signs of toxicity observed in animal studies have not been demonstrated in humans. At the levels of 2,3,7,8-TCDD encountered by humans in the environment, no adverse health effects other than chloracne have been demonstrated.

We submit that sufficient information has been gathered on the health effects of 2,3,7,8-TCDD to develop health effects levels for 2,3,7,8-TCDD and that, therefore, a relatively low priority should be placed on the additional studies proposed in the Draft Profile. Finally, the comments offer suggestions concerning the organization of the Draft Profile. These and other points are summarized below and are discussed in greater detail in the body of our comments.

ATSDR Should Determine Acceptable and Unacceptable Levels Of 2,3,7,8-TCDD

The focus of the Draft Profile is to summarize the considerable amount of data that have been generated concerning 2,3,7,8-TCDD and to provide narrative descriptions of the health impacts of exposure to 2,3,7,8-TCDD. While this is very beneficial, the Draft Profile would be of increased value if it went on to draw conclusions concerning the levels of 2,3,7,8-TCDD that reasonably pose risks to human health.

The process of developing health-based standards involves several steps. First, a toxicity standard for 2,3,7,8-TCDD should be developed to reflect its biological hazard. The toxicity standard would indicate the level of daily human intake of 2,3,7,8-TCDD that would present a minimal risk of adverse health effects. Second, exposure assessments should be undertaken to determine the amount of 2,3,7,8-TCDD that would be absorbed in the human body resulting from exposure to different types of contaminated sources. Finally, an acceptable level or concentration of 2,3,7,8-TCDD for a particular source would be determined by considering the toxicity standard and the exposure assessment. Acceptable levels or concentrations should be determined for each of those sources of 2,3,7,8-TCDD most likely to affect humans, such as contaminated fly ash, fish, and soil.

The time is ripe to draw conclusions concerning acceptable levels of 2,3,7,8-TCDD. The nature and health effects of 2,3,7,8-TCDD have been the subject of study and investigation by private and public entities and individuals for many years. Hundreds of articles and papers have been written and a large volume of data collected concerning the health effects of 2,3,7,8-TCDD on humans and other animals. A sufficient amount of information is available to undertake a sound analysis. Federal agencies in the United States, and governmental agencies in other countries, have developed conflicting conclusions on acceptable levels of 2,3,7,8-TCDD. There is a need to review independently the data and establish human health effect levels based upon the latest scientific understandings in order to address the uncertainties created by conflicting toxicity standards and to resolve the inconsistencies.

The development of acceptable levels of 2,3,7,8-TCDD could help resolve several important public issues, such as whether thermal processing or incineration should be used to manage municipal and hazardous waste. Some public and health officials are quite concerned about the levels of 2,3,7,8-TCDD that may be emitted from such devices. Information concerning the health risks posed by various levels of 2,3,7,8-TCDD would provide significant assistance in addressing these concerns.

The expanded scope of the Draft Profile that we propose is contemplated by the Superfund Amendments and Reauthorization Act (SARA) and by the Guidelines for Development of Toxicological Profiles (Guidelines), 52 Fed. Reg. 12870 et seq. (April 17, 1987) prepared by ATSDR and EPA. Section 110 of SARA provides that one of the three purposes of the Toxicological Profiles is to "...ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects." (Section 110 (1)(3)(A)). According to the Guidelines, the primary focus of the profiles is to meet this statutory objective such that "each profile will identify the quantity of a substance which represents a level of potential exposure that would constitute a public health concern based on available data." (52 Fed. Reg. 12872). Thus, both the statute and guidelines indicate that a primary function of the Toxicological Profiles is to set out the levels of a substance that produce a reasonable potential risk of adverse health effects.

ATSDR Should Not Adopt The Toxicity Standards and Exposure Calculations Used by EPA and CDC

The Draft Profile cites health effects levels that have previously been developed by other agencies. For example the Draft Profile sets out cancer risk estimations and Health Advisories for 2,3,7,8-TCDD in drinking water developed by EPA, and a level of concern for 2,3,7,8-TCDD in soil developed by Kimbrough et al. of CDC. However, these health effects levels are outdated. EPA and CDC are currently revising the cancer risk levels based upon new scientific data and analysis. We are concerned about the levels themselves and how they are presented in the Draft Profile. Most significantly, these levels should not be relied upon in the Draft Profile to satisfy the requirement that the toxicological profiles ascertain the levels of significant human exposure to 2,3,7,8-TCDD and the associated health effects.

The EPA and CDC levels referenced in the Draft Profile are based in significant part upon toxicity standards developed from the "linearized multistage model". This model is designed to calculate the cancer risk presented by substances that have no threshold dose for causing cancer. The model assumes that the substance to which it is applied causes cancer and that any dose presents a risk of cancer. Animal data based upon very high doses administered in the laboratory are used in the model to estimate the potential effect of extremely low doses encountered by humans in the environment.

In sharp contrast to the assumptions used in the linearized multistage model, the general consensus of the scientific community is that 2,3,7,8-TCDD has a threshold in humans, and a dose below that threshold poses no incremental risk of cancer. This consensus is based upon data showing that 2,3,7,8-TCDD causes no measurable alterations in DNA (and thus lacks mutagenicity), that 2,3,7,8-TCDD does not bind to DNA, and that 2,3,7,8-TCDD acts as a promoter when it causes cancer in laboratory animals. In addition, actual studies of past human exposure to 2,3,7,8-TCDD have not demonstrated that cancer resulted from such exposure. The available epidemiological evidence does not indicate that exposure to 2,3,7,8-TCDD has caused cancer in humans.

The weight of scientific opinion holds that the linearized multistage model, and other mathematical models that assume no threshold, is not appropriate for use in assessing the risk of 2,3,7,8-TCDD. The model significantly overestimates the actual health risks of 2,3,7,8-TCDD to humans. Thus, the health effect levels cited in the Draft Profile developed by EPA and CDC using the linearized multistage model are overly conservative and do not reflect the position endorsed by the general scientific community.

The unrealistically conservative nature of the levels generated by the linearized multistage model is dramatically demonstrated by current data on human background levels of 2,3,7,8-TCDD. Many researchers now estimate that there is a background level of 2,3,7,8-TCDD in the general population and that many people are exposed to about 1000 fg/kg/day of 2,3,7,8-TCDD from a variety of sources, including, as noted in the Draft Profile, exhaust from automobiles using leaded gasoline. This general level of 2,3,7,8-TCDD intake in industrial countries is over 150 times higher that the "safe" level estimated by EPA.

The health effects levels developed by EPA and CDC are also inconsistent. The EPA cancer risk levels and Health Advisories referenced in the Draft Profile are based, in part, upon a toxicity standard of 6 fg/kg/day. The level of concern developed by Kimbrough et al. of CDC is based upon a toxicity standard of 636 fg/kg/day. Both toxicity standards were developed using the linearized multistage model, but each agency calculated a much different standard. The Draft Profile also cites an advisory level established by the U.S. Food and Drug Administration for levels of 2,3,7,8-TCDD in edible portions of fish. This standard was calculated using a different approach and is consistent with a toxicity standard of 13,000 fg/kg/day.

The Draft Profile does not identify the purpose for listing the standards developed by other U.S. agencies, and it is unclear which of the conflicting standards, if any, is endorsed by ATSDR. If the purpose is simply to inform the reader, the final profile should identify the toxicity standards underlying the various calculations and should identify the additional standards developed by other countries. Information on standards developed by other U.S. agencies and by other countries is provided in the comments that follow. The Draft Profile should also explain that the levels calculated using the linearized multistage model are the product of assumptions concerning the cancer risk posed by 2,3,7,8-TCDD that are more conservative than those adopted by the general scientific community, that the calculations and assumptions are based upon old data, and that currently EPA and CDC are actively re-evaluating the cancer risk levels and levels of concern that they have previously calculated for 2,3,7,8-TCDD. As to EPA's cancer risk estimates, the final profile, consistent with requirements in EPA's risk assessment guidelines, should provide a complete and explicit disclosure of the scientific uncertainties and theoretical assumptions associated with the estimate. EPA itself stresses that the linearized multistage model "does not necessarily give a realistic prediction of the risk. The true value of the risk is unknown and may in fact be as low as zero." (EPA, 1986) This disclaimer should accompany any reference to EPA's cancer risk estimates in the profile.

The assumptions and caveats used in the risk assessment by Kimbrough et al. must also be described in order to give a more complete understanding of the significance and potential use of the resulting level of concern. While the Draft Profile indicates that the level applies only to residential soil, the final profile should also reflect the other assumptions employed by Kimbrough et al. , including the assumptions that 100% of the soil surface area is contaminated with 2,3,7,8-TCDD; that persons will spend a lifetime (70 years) in the contaminated area; and that children are present with a tendency to eat an abnormally large volume of soil.

Because the health effects levels developed by EPA and CDC are based upon assumptions that are no longer supported by the weight of opinion of the scientific community, we urge that ATSDR proceed beyond simply providing information on existing 2,3,7,8-TCDD health standards and critically evaluate the standards. The final profile should then proceed to reflect 2,3,7,8-TCDD health effect levels calculated by ATSDR using corrected assumptions and approaches.

ATSDR Should Calculate A Toxicity Factor Using The No Observed Adverse Effect Level For 2,3,7,8-TCDD

When ATSDR independently evaluates the data and quantifies the various levels of risk presented by 2,3,7,8-TCDD, it should not rely upon the linearized multistage model, or other mathematical models that assume no threshold, to establish a toxicity standard. A more appropriate approach is to evaluate information generated from animal research, as well as available human data, to determine the level of 2,3,7,8-TCDD that does not cause adverse health effects (No Observed Adverse Effect Level or NOAEL). This approach has been used by the U.S. Food and Drug Administration, the Canadian Province of Ontario, and several Western European countries in developing toxicity standards for 2,3,7,8-TCDD. It is the most widely accepted method for determining a toxicity standard for substances like 2,3,7,8-TCDD that are not cancer initiators and have threshold levels for adverse effects. Because the data used to establish a NOAEL came from animal research, a "safety factor" was added to the NOAEL when establishing a 2,3,7,8-TCDD toxicity standard for humans. The safety factors ranged from 100 (Province of Ontario) to 1000 (Federal Republic of Germany). A safety factor of 100 or more for 2,3,7,8-TCDD is not necessary because, among other reasons, a NOAEL can be developed by considering human health effects data.

The Draft Profile does set out four human health effect levels for 2,3,7,8-TCDD that were calculated by ATSDR. These levels pertain to the "minimal risks to humans for effects other than cancer". (Sections 1.6 and 2.2 and Figures 1.1 and 2.3). However, the Draft Profile does not explain the assumptions that were used in calculating the doses determined to present a "minimal risk" nor does it indicate whether the minimal risk levels are intended to constitute toxicity standards. To be of use to the public and governmental health officials, the methodology used to calculate the levels, the assumptions used in calculating the doses, the appropriate use for the resulting level, and the relationship between the minimal risk levels calculated by ATSDR and the health effects levels cited in the Draft Profile developed by other agencies must be thoroughly explained.

It appears that the minimal risk levels calculated by ATSDR may have been derived using a NOAEL rather than the linearized multistage model. If this is correct, we strongly support the approach. The resulting health effects levels should be explicitly preferred over the cancer risk levels previously developed by EPA.

The more detailed comments that follow provide additional information and references to assist in developing a NOAEL for 2,3,7,8-TCDD in humans. For example, the estimated daily uptake rate by "unexposed" individuals should result in a background body burden of at least 10 ppt. The profile should estimate daily uptake rates from the available body burden data in humans and from reported human exposures to 2,3,7,8-TCDD. References containing this information are identified in our comments. There is available adequate information to arrive at a sound NOAEL for 2,3,7,8-TCDD in humans.

ATSDR Should Undertake Exposure Assessments For Selected Sources Of 2,3,7,8-TCDD

In addition to determining a toxicity standard based upon a NOAEL, the Draft Profile should also reflect the results of exposure assessments of selected sources of human contact with 2,3,7,8-TCDD. These assessments are needed because the amount of 2,3,7,8-TCDD actually absorbed by the human body depends on the source of 2,3,7,8-TCDD exposure. The potential for exposure to, and absorption of, 2,3,7,8-TCDD varies significantly depending upon whether the 2,3,7,8-TCDD is in fish, soil, fly ash, etc. Exposure assessments, in conjunction with a toxicity standard establishing an acceptable human daily intake of 2,3,7,80-TCDD, will provide a basis for determining acceptable levels of 2,3,7,8-TCDD in various media. This will be valuable information for the public and governmental health officials when they are assessing site-specific environmental issues. The assumptions underlying the calculations should be clearly defined in order to allow the accurate application of acceptable levels to specific settings.

The Profile Should Be Consistent In Its Presentation That The Only Documented Effect Of 2,3,7,8-TCDD In Humans Is Chloracne

The effect of 2,3,7,8-TCDD on humans has been extensively investigated. Major epidemiology studies, as well as studies of occupational exposure, have not demonstrated any human health effects beyond chloracne. These studies have also demonstrated that chloracne is the most sensitive indicator of human exposure to 2,3,7,8-TCDD. No adverse health effects other than chloracne have been demonstrated at the levels of actual human exposure to 2,3,7,8-TCDD. There is an vast volume of negative data on human health effects other than chloracne.

The Draft Profile is clear in many sections that chloracne is the only demonstrated adverse human health effect resulting from exposure to 2,3,7,8-TCDD. We strongly support such statements, as well as statements indicating that there have been no reports of developmental toxicity, reproductive toxicity, genotoxicity, carcinogenicity, immunotoxicity, or death in humans as a result of exposure to 2,3,7,8-TCDD. We have provided additional references in the comments that follow to support these important conclusions.

While the Draft Profile states in many places that chloracne is the only demonstrated human health effect, there are references in other sections of the Draft Profile to "suggestive evidence" that 2,3,7,8-TCDD causes additional human health effects and that studies do not prove that 2,3,7,8-TCDD does not cause other effects. These allusions to other health effects are misleading, especially since some of the references appear in Section 1 of the Draft Profile (the Public Health Statement) which is intended for the general public. In the likely event that the public will generally read only Section 1 of the profile, the public will not have an accurate summary of the great volume of human health data that persuasively indicates that chloracne is the only proven adverse health effect. Thus, the profile should not allude to other potential human health effects, especially in Section 1, unless there is an accompanying explanation that, among all the individuals who have been exposed even to high levels of 2,3,7,8-TCDD, the only demonstrated human health effect resulting from exposure to 2,3,7,8-TCDD has been chloracne.

The final profile should also explain that the potential for adverse health effects is highly dependent upon the level or concentration of 2,3,7,8-TCDD exposure. As discussed above, the weight of scientific evidence indicates that there is a threshold dose below which there is no adverse health effect. It is only after exposure to high doses of 2,3,7,8-TCDD that chloracne has been demonstrated to occur in humans. Exposure to the high doses of 2,3,7,8-TCDD which resulted in chloracne have not resulted in any other demonstrated adverse human health effects.

Adverse human health effects are not expected to occur as a result of exposure to the levels of 2,3,7,8-TCDD present in the current or future environment. As provided by the Guidelines, a primary function of the profiles is "to evaluate the significance to individuals and the public-at-large of <u>current or potential</u> exposures to the subject hazardous substances" (emphasis added). (52 Fed. Reg. 12871). The human health data that was used in assessing health effects resulted, in large part, from high exposures to 2,3,7,8-TCDD that occurred in the past. These high levels of exposure do not occur at present and are not expected to occur in the future. The highest exposure levels to 2,3,7,8-TCDD in the past were directly or indirectly related to the production of herbicides and germicides contaminated with 2,3,7,8-TCDD. These exposures took place as a result of industrial accidents at plants manufacturing these chemicals (i.e., at Seveso, Italy and Nitro, West Virginia) or use of the contaminated chemicals (i.e., as defoliants in the U.S. and Vietnam). Because the herbicides and germicides contaminated with 2,3,7,8-TCDD are no longer being produced, exposures from these sources have been greatly reduced or eliminated. Since chloracne was the only demonstrated adverse human health effect resulting from the past high levels of exposure to 2,3,7,8-TCDD, adverse health effects are not expected to result from the lower current or potential levels of human exposure to 2,3,7,8-TCDD.

In addition, any reference to other human health effects should also explain that the "suggestive evidence" of effects other than chloracne consists of data from laboratory experiments with animals, and that the presence of adverse effects in laboratory animals does not necessarily mean that the adverse effects will be experienced in humans. For example, the doses given in the laboratory are not comparable to those encountered by humans in the environment. In dermal studies, a compound containing 2,3,7,8-TCDD is usually applied occluded in high doses to the skin of the animal for 24 or 48 hours. In the human environment, by contrast, skin is in contact with contaminated materials for a much shorter period of time, the contaminated material has a much lower concentration of 2,3,7,8-TCDD, and the contaminated material is rarely occluded. It has also been shown that human skin is less permeable to chemicals than animal skins. For these reasons, it is inappropriate to assume that the presence of animal health effects suggests the likelihood of any human health effects. Furthermore, the final profile should compare "absorbed" doses in humans and animals rather than comparing "administered" doses since the bioavailability of 2,3,7,8-TCDD varies considerably depending on the route of administration, the type of substance containing 2,3,7,8-TCDD, etc.

The Profile Should Specifically Indicate That Additional Studies Are Not Needed

One of the three major purposes for toxicological profiles as set out in SARA is to identify the toxicological testing "needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans." Section 100 (3)(C). This statutory requirement is reflected in the Guidelines, which provide that the profiles "will identify toxicological data needs for which research programs should be designed and initiated pursuant to the requirements of section 110 of SARA". 52 Fed. Reg. 12871. Along with quantification of risk, the development of a research program is a key purpose of the Toxicological Profiles.

We do not believe that additional research is needed to "identify the types or levels of exposure that may present significant risk of adverse health effects in humans." As discussed in the comments, there is a vast volume of accumulated data on 2,3,7,8-TCDD. There have been hundreds of papers published on the effects of 2,3,7,8-TCDD and a vast volume of data has been generated and evaluated. These data are sufficient to support sound assessments of the health effects of 2,3,7,8-TCDD and to develop toxicity standards and undertake exposure assessments. In light of the relatively limited human health effects of 2,3,7,8-TCDD and the lower current and future potential exposure levels, scarce research money is more productively used to assess chemicals that present a more significant and immediate concern to human health.

Comments on the Organization of the Profile

We agree that it is beneficial to include in the final profile a Public Health Statement designed to provide the general public with a concise statement of the general health risks associated with the substance. Consistent with the comments noted above and set out hereafter, the Public Health Statement for the Draft Profile should expand its current scope to include a summary of ATSDR's evaluation of the existing data and resulting quantitative assessment of the health effects of 2,3,7,8-TCDD. In order to provide the public with a good overall view of 2,3,7,8-TCDD, the Public Health Statement should also explain: (1) the dose-response relationship of 2,3,7,8-TCDD; (2) the conclusion that chloracne is the most sensitive indicator of 2,3,7,8-TCDD toxicity in humans; (3) the conclusion that adverse human health effects other than chloracne have not been demonstrated at the 2,3,7,8-TCDD levels encountered in the environment; and (4) the lessened potential for future exposure to 2,3,7,8-TCDD due to cessation of exposure from the manufacture and use of herbicides and germicides containing 2,3,7,8-TCDD as an impurity.

Figures 1.1 and 1.2 and the related narrative in subsequent sections of the profile subdivide human exposure and toxicity data by route of exposure (oral, dermal, and inhalation). However, most human exposures in real life situations occur, to a greater or lesser extent, by all three routes. In addition, overall human uptake of 2,3,7,8-TCDD is difficult to quantify. To attempt to quantify exposure on a route-specific basis unnecessarily complicates this task. We strongly recommend that all three routes of exposure be consolidated, rather than subdivided, in the graphic presentation and narrative analysis of human exposure and toxicity data.

Figures 2.5 and 2.6, which are intended to summarize the adequacy of the existing data, are not particularly useful. There have been extensive studies of 2,3,7,8-TCDD over a long period of time. Much more is known about 2,3,7,8-TCDD than is know about many other toxic substances. Merely indicating the general areas where even more data on 2,3,7,8-TCDD could be collected serves no real purpose. What is important is that there is currently available sufficient data to support sound assessments of the health effects of 2,3,7,8-TCDD and to develop toxicity standards and undertake exposure estimates. In addition, Figure 2.5 gives the impression that all the data that is known about the toxicity of 2,3,7,8-TCDD in humans is by the dermal route of exposure and that there is no human data by the oral and inhalation routes. As explained above, this mischaracterizes what is known about 2,3,7,8-TCDD exposure and would tend to mislead the general public.

The detailed comments that follow expand upon many of the points made in this Summary. The comments also, among other things, provide additional references to support many of the conclusions reflected in the Draft Profile and to assist ATSDR in developing a NOAEL for 2,3,7,8-TCDD toxicity in humans.

CMH/8413X

COMMENTS ON THE DRAFT TOXICOLOGICAL PROFILE FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

1. PUBLIC HEALTH STATEMENT

Syntex Agribusiness, Inc. ("Syntex") agrees that the format of the Public Health Statement is a valuable way to convey key information to the public, and endorses the purpose of the Public Health Statement, as described in the Guidelines,

> The section of the profile, if removed from the rest of the document, should still be capable of conveying to the general lay public the substantive public health concerns associated with this substance (52 Fed. Reg. 12873).

In light of this very important purpose, Syntex offers suggestions in the comments that follow to ensure, among other things, consistency between the Public Health Statement and the more detailed subsequent sections of the Draft Toxicological Profile for 2,3,7,8-Tetrachlorodibenzo-p-dioxin ("Draft Profile").

As discussed in the introduction to its comments, Syntex urges ATSDR to develop a health-based toxicity standard and to conduct exposure assessments in order to develop levels of 2,3,7,8-TCDD considered safe in selected sources of potential human exposure to 2,3,7,8-TCDD. It would be useful to include a section in the Public Health Statement setting forth ATSDR's overall interpretation of the available information on 2,3,7,8-TCDD, including ATSDR's views on what constitute unacceptable levels of human exposure to 2,3,7,8-TCDD.

1.1 What is dioxin?

The assertion in Section 1.1 that 2,3,7,8-TCDD does not occur naturally should be modified since Bumb _et al_. (1980) indicated that chlorinated dioxins can result from trace chemical reactions occurring in the combustion of most organic material such as forest fires. References to the inadvertent production of 2,3,7,8-TCDD during the manufacture of certain herbicides and germicides should be stated in the _past tense_ since these products are no longer manufactured.

1.2 How might I be exposed to 2,3,7,8-TCDD?

The value of this section to the general lay public is to provide information about the sources of potential 2,3,7,8-TCDD exposure in order to enable the public to make judgments about what activities or environmental situations could be cause for concern. To accomplish this purpose, the Draft Profile should state at the outset that there exists a measurable "background" body burden level of 2,3,7,8-TCDD in the U.S. population and in populations in other industrialized countries around the world. This section should also indicate that it is only when 2,3,7,8-TCDD exposure reaches unacceptable concentrations that it poses a concern for human health. In its description of the major sources of contamination of 2,3,7,8-TCDD, the Draft Profile should also summarize the relative potential and magnitude of human exposure to 2,3,7,8-TCDD resulting from these sources. The following comments focus upon the sources of potential 2,3,7,8-TCDD contamination listed in Section 1.2 and include suggestions on their relative potential for resulting in adverse human health effects.

The substances 2,4,5-trichlorophenol, 2,4,5-T, and hexachlorophene are listed in Section 1.2 as environmental sources of 2,3,7,8-TCDD. Because the production and use of these substances have been banned, their listing should be qualified by stating, "Environmental contamination from past production and use of . . . ". In addition to the other sources of environmental contamination listed, the bleaching process in the paper industry has been found to produce chlorinated dioxins (Kuehl et al., 1987).

In the paragraph discussing environmental sources of 2,3,7,8-TCDD, some idea of the limit of detection in ambient air and drinking water should be presented as well as better quantification of what is meant by "trace levels" in normal urban soil. It is uninformative to compare 2,3,7,8-TCDD levels in Missouri soil to trace levels in normal urban areas when these "trace" levels are not identified in the Draft Profile.

The Draft Profile's reference to 2,3,7,8-TCDD levels in contaminated Missouri soil is misleading, especially since the purpose of this section is to inform the public of potential sources of 2,3,7,8-TCDD exposure. The 2,3,7,8-TCDD level in Missouri soil that is "a million times higher" than soils in normal urban areas pertains only to isolated "hot spots" and is not representative of the average level found in the contaminated areas. The general public does not even have access to some of these contaminated areas. If the purpose of the reference is to inform the public of a potential source of exposure, the level of contamination should be based upon the average concentration of 2,3,7,8-TCDD at contaminated sites. On the other hand, if the purpose of the reference is to present the high end of a range of 2,3,7,8-TCDD contamination, the reference should note this purpose and should be accompanied by the observation in Section 1.6 that the exposure of Missouri residents to 2,3,7,8-TCDD has not been demonstrated to have produced chloracne or any other adverse health effect. (Knutsen et al., 1987; Webb et al., 1987; Stockbauer et al., in press).

Some consumer sources of 2,3,7,8-TCDD appear inconsistent with statements in the preceding paragraph. If exposure to certain consumer sources has not been documented, then they should be qualified as "potential" consumer sources. For example, if 2,3,7,8-TCDD has not been detected in human milk in the U.S., it should not be listed as a consumer source of 2,3,7,8-TCDD. If

2,3,7,8-TCDD has not been detected in any other foods besides fish, the consumption of root vegetables, livestock, and cow's milk should not be listed as consumer sources of 2,3,7,8-TCDD. The last point under consumer sources, which concerns 2,4,5-T-containing herbicides and hexachlorophene, should be deleted from this paragraph and inserted under environmental sources of 2,3,7,8-TCDD.

Under occupational sources of 2,3,7,8-TCDD exposure, both the first and last points should be qualified to indicate that these occupations have been discontinued. Occupational exposure of workers in the paper industry should be added.

Providing information on the relative amounts of 2,3,7,8-TCDD originating from or located in various sources, and basing those amounts on levels that are reasonably expected to be encountered by the public, is consistent with the Guidelines for Development of Toxicological Profiles, 52 Fed. Reg. 12870 et seq. (April 17, 1987). The Guidelines provide that a "primary function of the profiles" is to present and interpret data which may be used to "evaluate the significance to individuals and the public-at-large of current or potential exposures to the subject hazardous substances." (52 Fed. Reg. 12871). Section 1.2 should summarize information which would allow the public to evaluate the significance of current or potential exposures to 2,3,7,8-TCDD.

1.3 How does 2,3,7,8-TCDD get into my body?

This section provides a valuable link between Section 1.2 (Sources of Exposure) and Sections 1.4 and 1.6 (Health Effects). To increase the public's understanding of the relationship between exposure and uptake and potential health effects, Syntex suggests that this section contain a brief narrative explaining the three major routes of uptake into the body (ingestion, dermal absorption, and inhalation), the relative magnitude of uptake by each route, and the major factors that affect uptake, e.g., duration of exposure, medium of exposure, level of exposure, etc. Because the general public often equates exposure with adverse effects, it could misinterpret the statement that "inhalation of particulates such as fly ash, however, may constitute a major source of exposure." (Emphasis added) The consequences of such exposure is minimal given the low levels of 2,3,7,8-TCDD in fly ash. Providing the magnitude and significance of potential 2,3,7,8-TCDD exposure from the various sources would help avoid this type of misinterpretation. In addition, Syntex suggests the deletion of references to "cow's milk and foodstuffs" since the Draft Profile indicates in other sections that 2,3,7,8-TCDD has not been found in these items. See, for example, section 1.2 and Chapter 7.

1.4 How can 2,3,7,8-TCDD affect my health?

Syntex agrees with statements located in various sections of the Draft Profile that chloracne is the only demonstrated adverse health effect in humans that has resulted from exposure to 2,3,7,8-TCDD. A review of the literature indicates that in humans, chloracne is the most sensitive and the only documented health effect caused by exposure to 2,3,7,8-TCDD (Suskind, 1985). No other adverse human health effect resulting from exposure to 2,3,7,8-TCDD has been demonstrated.

Chloracne has been found only in certain industrially exposed workers and in some residents at Seveso, Italy, after an industrial explosion. No chloracne cases have been reported from other environmental exposures to 2,3,7,8-TCDD. Because the production of 2,3,7,8-TCDD-contaminated herbicides and hexachlorophene has been banned, the likelihood of seeing new cases of chloracne from occupational 2,3,7,8-TCDD exposure is remote.

In the discussion of other potential adverse health effects resulting from exposure to 2,3,7,8-TCDD, Section 1.4 uses such phrases as "suggestive evidence" and "never demonstrated in humans". The use of the phrase "suggestive evidence" is both confusing and inconsistent with the more detailed discussions in subsequent sections of the Draft Profile. For example, use of the phrase, "suggestive evidence" in conjunction with "liver damage in humans, as indicated by an increase in levels of certain liver enzymes in the blood" is confusing because the Draft Profile states in Section 1.5, paragraph one, that while there is a blood test capable of detecting certain enzymes associated with liver damage, these tests "do not indicate with certainty that you have been exposed to 2,3,7,8-TCDD, since other chemicals, as well as drinking alcohol, can cause similar results." Use of the phrase "suggestive evidence" also creates an apparent inconsistency with the more detailed sections of the Draft Profile that follow. For example, Section 1.4 indicates that there is "suggestive evidence" that 2,3,7,8-TCDD causes liver damage in humans. However, Section 2.2.2 states that "other signs of toxicity observed in animal studies (i.e., liver damage...) have not been demonstrated in humans and are not useful in determining that exposure to 2,3,7,8-TCDD has occurred." (emphasis added) In order to eliminate the potential confusion and to ensure consistency with other sections of the Draft Profile, Syntex recommends that points 2 through 7 in Section 1.4 be reworded to indicate that none of these adverse health effects has been demonstrated in humans.

Section 1.4 should also indicate that other than chloracne, no other adverse health effect, including cancer, has been demonstrated to result from human exposure to 2,3,7,8-TCDD. In addition, not one human death has been attributed to exposure to 2,3,7,8-TCDD.

Discussion of the toxicity of a chemical must include reference to exposure. Therefore, ATSDR should take the opportunity to educate the reader on the concept of dose-response in this section.

1.5 Is there a medical test to determine whether I have been exposed to 2,3,7,8-TCDD?

For the reasons discussed below, we suggest that paragraph one of Section 1.5 be dropped.

Paragraph one states that "It is believed that a blood test to detect certain enzymes indicating liver damage may be helpful in determining whether exposure has occurred." Presumably, this is a reference to enzymes such as SGOT, SGPT, LDH, etc. The quoted sentence makes little sense because, as discussed elsewhere in the Draft Profile, liver damage in humans resulting from exposure to 2,3,7,8-TCDD has never been demonstrated, see Section 2.2.2. The Draft Profile also correctly points out that elevation of these blood enzymes, while indicative of hepatic injury, is too non-specific to be helpful in identifying whether exposure to 2,3,7,8-TCDD has occurred. If the Draft Profile is referring to the "enzyme induction" effect of 2,3,7,8-TCDD, this effect cannot be detected by monitoring blood enzyme levels since these enzymes remain inside the liver cells. Furthermore, enzyme induction is not considered an adverse effect unless the chemical in question is metabolized to more toxic intermediates, which is clearly not the case with 2,3,7,8-TCDD.

Paragraph one is also inconsistent with the style of some of the other Draft Profiles, e.g., those on chloroform and benzo(a)pyrene, where there also is no common medical test available to "demonstrate unequivocally" exposure. The other Draft Profiles report tests, routine or non-routine, which can be done to determine whether one has been exposed to the chemical in question. Tests to accomplish this purpose are also available for 2,3,7,8-TCDD. See our comments on Section 2.2.2.

2,3,7,8-TCDD can be measured in blood and in adipose tissue. While these tests are not routinely performed due to cost and complexity of analysis, they have provided information on the body burden levels of 2,3,7,8-TCDD in "exposed" and "non-exposed" (background) populations (Graham et al., 1985, 1986, submitted; Ryan et al., 1985; Stanley et al., 1986). The measurement of 2,3,7,8-TCDD levels in serum lipids will undoubtedly be used widely to evaluate past human exposure, but cannot be used to evaluate potential future exposure. Potential future exposure of an individual to 2,3,7,8-TCDD can be estimated if one knows the extent of 2,3,7,8-TCDD contamination in the various media and foodstuffs to which the person is exposed and the amount of each that is taken up by him.

1.6 What levels of exposure by ingestion and by skin contact have resulted in harmful health effects?

Syntex offers the following suggestions concerning Figures 1.1 and 1.2, which are an effective means for displaying the data available in animals and humans. The data underlying the graphs would be more accurately represented if the extrapolated values for minimal risk of effects other than cancer for humans were presented on separate graphs. Otherwise, these dose levels can easily be misinterpreted as levels determined experimentally, as is the case for animal effects. In addition, the format of dividing exposure by routes of uptake as shown in Figs. 1.1 and 1.2 is problematical in that human exposure invariably includes uptake by all three routes. The overall uptake is difficult enough to quantify. Attempts to quantify exposure on a route-specific basis is even more difficult. This becomes more apparent in subsequent sections of the Draft Profile that discuss 2,3,7,8-TCDD's toxicity, which again ATSDR has subdivided by route of exposure. A better approach to presenting human exposure and toxicity data would be to display exposure in terms of the total amount of 2,3,7,8-TCDD absorbed into the body by all routes of exposure, modifying the administered dose by the bioavailability for each route (or media).

Because the Public Health Statement is designed to stand alone and will no doubt reach a larger audience, an explanation of the bases of the dose levels of each endpoint should be included. The extrapolated values for humans should be mentioned in the text, along with an explanation of how these levels were derived. It appears that the dose corresponding to the "minimal risk for effects other than cancer" after long-term exposure was derived using a LOAEL of 1 ng/kg/day as calculated by Nisbet and Paxton (1982) upon their re-evaluation of the three-generation rat study of Murray et al. (1979), and applying a safety factor of 1000.

Nisbet and Paxton's re-evaluation and resultant value for the LOAEL is not universally accepted because of flaws in the statistical methodologies that they used. For instance, they combined all of the animals in the three-generation study and considered the effect of 2,3,7,8-TCDD on each animal to occur independently of one another. As pointed out by Kimbrough et al. (1984), it is incorrect to combine animals from different generations because animals from one generation can have an effect on animals of the next generation. Thus, the effects observed in animals of one generation cannot be considered independent of the effects observed in animals of subsequent generations. For this reason, Kimbrough et al. (1984) reaffirmed the conclusion of Murray et al. (1979) that the LOAEL was 10 ng/kg/day and the NOAEL was 1 ng/kg/day. The Ontario ministry of the Environment also concluded that the NOAEL, rather than the LOAEL, was 1 ng/kg/day (OME, 1985). Thus, ATSDR should apply the conclusion of the original authors that the LOAEL is 10 ng/kg/day and the NOAEL is 1 ng/kg/day.

A critical study which ATSDR should evaluate is the Kligman study using prisoners (as cited in Rowe, 1980). A dose in humans which causes chloracne can be calculated from his study and displayed in Fig. 1.2. Another study which can contribute points to Fig. 1.2 is Patterson et al. (1986). That study found no chloracne in workers with up to 750 ppt of 2,3,7,8-TCDD in their adipose tissue 15 years after exposure had ceased. ATSDR should also consider Byard (1987), which reviewed the data regarding 2,3,7,8-TCDD levels in human adipose tissue data and their relationship to toxicity.

As mentioned in the previous section, a background body burden of 2,3,7,8-TCDD (averaging approximately 10 ppt) has been found in the general "unexposed" population. Certainly, exposure to 2,3,7,8-TCDD that results in this background body burden is not believed to cause adverse effects, i.e., this can be considered a minimum NOAEL in humans. An estimation of the maximum NOAEL in humans is also useful. It has been reported that ingestion of typical diets in Sweden and Japan results in a 2,3,7,8-TCDD uptake of 1.0 pg/kg/day (Ono et al., 1986), and in the U.S., an uptake of 0.7 pg/kg/day (Travis and Hattemer-Frey, in press). Commoner et al. (1986) has estimated that a daily dose of 1.0 pg/kg/day is needed to maintain a body burden of 10 ppt in adipose tissue. There is a considerable amount of data on human body burdens (as surrogate of exposure) which ATSDR could incorporate into its discussion in Section 1.6 and in Fig. 1.1 and 1.2.

Because Section 1.6 pertains to levels of exposure that "have resulted in harmful health effects" (emphasis added), it should not include a discussion of cancer in humans. Extensive studies of human populations exposed to relatively high levels of 2,3,7,8-TCDD have not demonstrated that human exposure to 2,3,7,8-TCDD results in cancer. The general consensus of the scientific community is that 2,3,7,8-TCDD lacks mutagenicity and is not genotoxic. The reference to EPA's cancer risk estimate in Section 1.6 should therefore be omitted. If the cancer risk estimate is discussed in another section, then the following comments would be applicable.

The Draft Profile should explain the cancer policy of EPA, which includes the position that any exposure to a carcinogen (initiator or promoter) is accompanied by some level of risk. Consequently, EPA considers it necessary to express the likelihood of developing cancer in terms of a dose corresponding to that level of risk. EPA calls the dose that corresponds to an acceptable level of such risk the "Virtually Safe Dose" (VSD). Although the evidence that 2,3,7,8-TCDD causes cancer in humans is inadequate (IARC, 1982; EPA, 1985a), EPA has developed a mathematical model to quantify the theoretical risk of developing cancer, on the assumption that 2,3,7,8-TCDD can indeed cause cancer in humans at any dose. The dose corresponding to a theoretical one-in-one-million risk of cancer was estimated by EPA to be 6 fg/kg/day. The appropriateness of EPA's mathematical model and the relevancy of using a 10^{-6} risk value have been criticized (Sielken, 1987; AIHC, 1985; Rodricks et al., 1987; Travis et al., 1987).

It should also be pointed out that although the EPA has adopted a 10^{-6} risk as the acceptable degree of risk for 2,3,7,8-TCDD (EPA, 1985a), this degree of risk is neither stipulated by Superfund Guidelines (EPA, 1985b), nor realistic when compared with other risks associated with life in an industrialized society. The Superfund Guidelines, in fact, state that 10^{-4} to 10^{-7} risk may be used. More importantly, the Guidelines recommend incorporation of site specific-factors.

According to EPA policy, the target total individual carcinogenic risk resulting from exposures at a Superfund site may range anywhere between 10^{-4} to 10^{-7}. Thus, remedial alternatives should be able, under existing EPA policy, to reduce total potential carcinogenic risks to individuals to levels within this range.

This range (10^{-4} to 10^{-7}) of cancer risks was intended primarily for use in populations exceeding 100,000 persons. For populations of from less than 100,000 to several million persons, EPA often has adopted other risk criteria where the risk "trigger" is one theoretical incidence of cancer in a population of 10,000 rather than an individual risk of 1 in 1,000,000. A sensitivity to the size of the exposed population has been considered appropriate in risk assessment, since it would be unreasonable and wasteful to invest large sums of money to protect only a handful of persons from a low probability event, thereby diverting resources from protection against risks to which large numbers of persons are exposed. Specifically, in the case of a risk of 10^{-4}, more than 10,000 persons would need to be exposed at that particular level for a lifetime in order to encounter one theoretical case. EPA on numerous occasions has chosen not to regulate risks in situations where small numbers of persons were exposed and less than one theoretical incident was expected as a result of the exposure (Paustenbach, 1987).

By reason of inadequacies in EPA's mathematical model and the general consensus that 2,3,7,8-TCDD acts by a promoter mechanism, EPA is currently reviewing it standard, and an internal Agency committee has recommended that the standard be revised from from 6 fg/kg/day to at least 100 fg/kg/day. The Draft Profile should make this known to the reader. It should also refer to the 2,3,7,8-TCDD standards set by other U.S. agencies and by other countries around the world (see table on page 18).

Comparison of Allowable TCDD Intake Calculated by Governmental Agencies

Agency	Risk-analysis Approach	Allowable TCDD intake (fg/kg/day)
EPA[a]	Linearized multistage	6.4
CDC[b]	Linearized multistage	28-1428
SINH[c]	Safety factor (250)	4,000
OME[d]	Safety factor (100)	10,000
FEA[e]	Safety factor (100-1000)	1000-10,000
FDA[f]	Safety factor (77)	13,000

[a]EPA, (1985a)

[b]Kimbrough _et al._ (1984)

[c]Vander Heijden _et al._ (1982)

[d]Ontario Ministry of the Environment (1985)

[e]Federal Environmental Agency (1984)

[f]Cordle (1981)

(from Shu _et al._, 1987)

Finally, EPA itself stresses that the mathematical model it uses to estimate cancer risks "does not necessarily give a realistic prediction of the risk. The true value is unknown and may in fact be as low as zero." (EPA, 1986). This statement should accompany any reference in the Draft Profile to EPA's cancer risk estimate.

1.7 What recommendations has the federal government made to protect human health?

It should be pointed out that EPA's and IARC's statement that "2,3,7,8-TCDD may cause cancer in humans" should be interpreted as a "regulatory" position and not "biological" certainty. It has not been demonstrated that cancer in humans has been caused by 2,3,7,8-TCDD exposure. These agencies categorize 2,3,7,8-TCDD as such only for regulatory purposes, after consideration of theoretical risks.

ATSDR should explain the basis of EPA's Health Advisories for 2,3,7,8-TCDD in drinking water. The EPA Health Advisory for 2,3,7,8-TCDD in water is based upon a Virtually Safe Dose (VSD) of 6 fg/kg/day, which is the most conservative VSD that has been suggested that "might" produce a risk of cancer of one-in-one-million following a lifetime of exposure (EPA, 1985a). Other U.S. governmental agencies, Canada, the Netherlands, and Germany have suggested that a VSD or Acceptable Daily Intake of between 4,000 to 13,000 fg/kg/day is more reasonable. (The Table on page 18 of our comments).

The EPA Health Advisory is also based upon several other overly conservative assumptions, including the assumption that everyone will drink 2 liters of contaminated water each day. EPA is reconsidering its adoption of 6 fg/kg/day in light of data and analyses developed since the adoption of that number. At a minimum, Section 1.7 should explain that the EPA Health Advisory is the product of assumptions concerning the cancer risk posed by 2,3,7,8-TCDD, that these assumptions are more conservative than those adopted by the general scientific and regulatory community, that these assumptions are based upon old data, and that the VSD of 6 fg/kg/day is currently being re-evaluated by EPA. A table summarizing the standards set by the various regulatory agencies in the U.S. and elsewhere, along with the rationale for the standards, would be helpful. Most importantly, ATSDR should add a section stating its own position on how 2,3,7,8-TCDD should be regulated, rather than only noting what other agencies have done in the past.

Finally, some of the values presented in mg/L do not correspond to the values in ppt. For instance, the one-day Health Advisory of 0.000001 mg/L corresponds to 1 ppt, not 10 ppt, and the ten-day Health Advisory of 0.00000001 mg/L corresponds to 0.01 ppt, not 0.001 ppt.

2.2 Levels of Significant Exposure

The second paragraph in this section states:

> These minimal risk levels were derived for the most sensitive noncancer end point for each exposure duration by applying uncertainty factors.

The Draft Profile should state what these uncertainty factors are and should state the rationale for using them. Furthermore, the Draft Profile should make clear what is meant by "minimal risk level." Applying uncertainty factors to a NOAEL or LOAEL derived from animal data generally implies that the resultant value is equivalent to a NOAEL in humans. The Draft Profile should indicate whether the minimal risk levels are synonymous with a NOAEL in humans. While this phrase is defined in the Glossary, it should also be defined at least in the text where it first appears.

The issue of differential bioavailabilities from different media should be addressed in this section. Human exposure is primarily to 2,3,7,8-TCDD adsorbed onto soil or fly ash, where the bioavailability is lower than that of 2,3,7,8-TCDD in feed or in lipophilic vehicles administered to animals. Exposure by humans to levels corresponding to ATSDR's estimated minimal risk level would actually result in a lower uptake of 2,3,7,8-TCDD since exposure would primarily be to media with lower bioavailabilities. To address this issue, ATSDR should clarify the difference between "administered dose" and "absorbed dose."

The reference in Section 2.2 to estimated human cancer risk level should be accompanied by an explanation of the estimate. EPA's risk assessment Guidelines provide that references to the Agency's risk estimates must furnish a complete and explicit disclosure of the scientific uncertainties, theoretical assumptions, and range of risks associated with the estimates. The explanation should emphasize that the estimates represent only an upper limit to risk; that the risk may be as low as zero; and that it is the weight of scientific opinion that the model used to calculate the estimates is inappropriate for estimating the human cancer risk presented by 2,3,7,8-TCDD. Contrary to the assumptions used by the model, the general consensus of the scientific community is that 2,3,7,8-TCDD acts by a tumor promotion mechanism (Pitot Committee Report, 1986). The explanation should also mention that EPA is currently re-evaluating its own 2,3,7,8-TCDD human cancer risk assessment.

The estimated human cancer risk levels on Fig. 2.3 do not appear to correspond to the appropriate dose levels. If one were to accept the conclusions presented on page 16, then a 10^{-4} risk should correspond to a dose of 0.6 pg/kg/day. Fig. 2.3 shows a 10^{-4} risk corresponding to 1.0 fg/kg/day.

2.2.1 Key Studies and Graphical Presentations

There are several sources of data which can be used to assess the risk to humans from 2,3,7,8-TCDD exposure. One key study which has been omitted is the Kligman study using prisoners (as cited in Rowe, 1980). This study supports the Draft Profile's conclusion that chloracne is the most sensitive indicator of toxicity in humans and provides useful insight on the relative sensitivity of humans to 2,3,7,8-TCDD toxicity as compared to animals. The Kligman study provides data points which can be placed on Fig. 2.2. In addition, the self-dosing study of Poiger and Schlatter (1986) provides a NOAEL for Fig. 2.1.

A woman from Seveso, Italy, had a body burden of 40 µg of 2,3,7,8-TCDD (Reggiani, 1981 as cited in Young, 1984) with no reported adverse effects attributed to this level. A NOAEL can be calculated by estimating her body weight. Her exposure would have been by all routes of exposure and thus would be appropriate for inclusion on a graph considering all routes of exposure. Except for Kligman (as cited in Rowe, 1980), and Poiger and Schlatter (1986), all human exposures occur by multiple routes.

With new analytical methodologies to measure the body burden of 2,3,7,8-TCDD in humans, human body burdens can be converted to daily doses and plotted on the graphs. ATSDR should not wait for data on human exposure any more precise than what is available unless experimental research on humans is conducted, a very unlikely possibility. At the very least, the background body burden level of 2,3,7,8-TCDD would certainly represent a NOAEL and should be converted to a daily dose. Approaches for converting body burdens to daily doses have been proposed by Gehring (1984) and Commoner et al. (1986).

2.2.1.2 Oral

Syntex agrees with the statement under the subheadings for Lethality and Decreased Longevity, Developmental Toxicity, Reproductive Toxicity, Genotoxicity, and Carcinogenicity that there has been no documentation of such effects in humans as a result of oral exposure to 2,3,7,8-TCDD. To ensure consistency, the second sentence under Lethality and Decreased Longevity should indicate that "2,3,7,8-TCDD is highly toxic to all non-human mammalian species...". In addition, a statement such as, "There have been no reports of target organ toxicity in humans as a result of oral exposure to 2,3,7,8-TCDD" should be added under the subheading Target Organ/Systemic Toxicity. Syntex believes the discussion of target organ toxicity on pages 14-16 refers to effects observed in animals. The Draft Profile should make clear that the four major toxic effects characteristic of 2,3,7,8-TCDD (chloracne, wasting syndrome, hepatotoxicity, and immunotoxicity) pertain to animals and not to humans (except, of course, for chloracne).

The second sentence under Target Organ/Systemic Toxicity, which lists numerous adverse health effects that "have been observed in humans exposed to chemicals contaminated with 2,3,7,8-TCDD", is very misleading. The chemicals contaminated with 2,3,7,8-TCDD, rather than the 2,3,7,8-TCDD itself, is the most likely explanation for any observed adverse effects. To be consistent with the overall conclusion of the Draft Profile that chloracne is the only demonstrated adverse health effect of 2,3,7,8-TCDD in humans, the second sentence referenced above should be omitted, or at least qualified by emphasizing that the effects have not been demonstrated to be caused by 2,3,7,8-TCDD.

On page 14, third paragraph, the Draft Profile states that the minimal risk for effects after acute oral exposure was calculated by EPA (1985a). For critical issues such as the setting of the minimal risk level, ATSDR should explain the approach used to calculate the level rather than cite a reference. In addition, ATSDR should clarify what is meant by "minimal risk."

Similarly, on page 15 under the Reproductive Toxicity subheading, ATSDR cites EPA (1985a) as the source for calculating the minimal risk level from intermediate and chronic oral exposure. Again, the meaning of minimal risk level should be explained. The exact approach that EPA took should be described in the Draft Profile.

Under the Genotoxicity subheading, it is inaccurate to state that the inconsistencies observed for the lack of genotoxicity of 2,3,7,8-TCDD may be related to the low solubility and high toxicity of 2,3,7,8-TCDD rather than to its inherent biological inactivity in the systems tested. On the contrary, 2,3,7,8-TCDD is considered non-genotoxic because of well conducted negative studies, the non-reproducibility of the few positive studies, and the inappropriate methodologies used in the studies that were positive (Kociba, 1984; IARC, 1982; Fishbein, 1987; Shu et al., 1987).

On page 16, under the Carcinogenicity subheading, ATSDR describes EPA's approach for calculating q_1^*. This lets the reader know what has taken place without having to go back to a reference. EPA's approach for estimating q_1^* has been criticized for its ultraconservatism (see previous comments).

2.2.1.3 Dermal

The section and heading "2.2.1.3 Dermal" should be added before the "Lethality and Decreased Longevity" subheading on page 16 of the Draft Profile.

The rabbit LD_{50} of 275 µg/kg has been displayed in Fig. 2.4 to be between 1,000 and 10,000 µg/kg/day. It should be between 100 and 1,000 µg/kg/day.

There is no convincing evidence to indicate that human exposure occurred primarily by the dermal route, as ATSDR appears to assume (since the human studies are described under this section rather than under section 2.2.1.2).

On page 16 under the Target Organ/Systemic Toxicity subheading, the Draft Profile indicates that there is no information on the levels of exposure needed to produce chloracne in humans, and that, therefore, quantitative risk assessments cannot be done. Syntex believes that such data is available and that sufficient information exists to perform a sound risk assessment. See, for example, Syntex comments on sections 2.2.1 and 4.3.1.3.

Pages 16 and 17 of the Draft Profile indicate that there are data that suggest 2,3,7,8-TCDD causes adverse liver and reproductive effects in humans. Syntex believes that if ATSDR critically evaluates each of these studies, it will conclude that factors other than 2,3,7,8-TCDD are responsible for the reported adverse effects.

Syntex agrees with ATSDR's conclusion on page 3 of the draft profile that impairment of the immune system in humans has not been demonstrated. This conclusion should be summarized in section 2.2.1.3 of the draft profile.

There are many studies that support the conclusion that 2,3,7,8-TCDD has not been demonstrated to be toxic to the human immune system. Not only did the study of Missouri residents show no impairment of immune function (Harmon, 1987; Evans et al., 1987), but also studies of Seveso residents (Reggiani, 1980; Sirchia et al., 1982a,b) and the Ranch Hand group (Lathrop et al., 1984, 1987) were negative.

If the epidemiologic studies on cancer are taken as a whole, the conclusion would be that past 2,3,7,8-TCDD exposures did not cause cancer. In the most highly exposed groups, those of occupational workers, Vietnam veterans, and Seveso residents, no statistically significant increase in the cancer incidence was found.

The general consensus of the scientific community is that 2,3,7,8-TCDD is a tumor promoter in animals (Pitot Committee Report, 1986; U.S. EPA Promoter Workshop, 1987b). Evidence supporting the conclusion that 2,3,7,8-TCDD is a tumor promoter in animals includes: (1) its lack of genotoxicity (Kociba, 1984; IARC, 1982; Fishbein, 1987; Shu et al., 1987), (2) its lack of covalent binding to nucleic acids (Guenthner et al., 1979; Poland and Glover, 1979); and (3) positive results in the classic tumor promotion experiments (Pitot et al., 1980; Poland et al., 1982).

2.2.2 Biological Monitoring as a Measure of Exposure and Effects

The analysis of adipose tissue and blood for 2,3,7,8-TCDD _is_ a reliable indicator of past exposure. Discrepancies in the past may have been a result of analytical methodological errors or the inability to identify those individuals who had been heavily exposed (Korgeski and Leon, 1983; Stellman and Stellman, 1986; Hardell _et al_., 1985).

It is true that data on the correlation between the body burden of 2,3,7,8-TCDD and of exposure (daily exposure rates) are lacking. However, with the more precise data on the biological half-life in humans (CDC, 1987b), and with improvements over the procedure suggested by Gehring (1984) and Commoner _et al_. (1986) for calculating this type of conversion, a good estimate of what the body burden can now be made if the daily dose is known, and a good estimate of daily dose can be made if the body burden is known.

Although page 19 of the Draft Profile indicates that there is a lack of correlation between environmental levels and estimated human exposure to 2,3,7,8-TCDD, a likely explanation is simply that Vietnam veterans were not highly exposed to Agent Orange. This conclusion is consistent with the findings of the Ranch Hand study and other studies of Vietnam veterans, where essentially no adverse health effects were reported (Lathrop _et al_., 1983, 1984, 1987).

We agree with ATSDR's statement on p. 19 that:

> Chloracne is the only effect that is clearly associated with exposure to chemicals contaminated with 2,3,7,8-TCDD.

We disagree with a subsequent statement in the same section that:

> ...the data of Hoffman et al. (1986) suggest that the development of immunotoxicity would provide supportive evidence for exposure to 2,3,7,8-TCDD.

A follow-up study to reassess the immune function in the group that Hoffman et al. studied revealed no impairment of immune function (Harmon, 1987; Evans et al., 1987). In light of the follow-up study, the data in question do not support the quoted statement, and the statement should therefore be omitted.

2.2.3.1 Levels found in the environment

There are numerous incidents where humans have been exposed to 2,3,7,8-TCDD without producing any documented adverse health effects. An estimation of the levels of 2,3,7,8-TCDD exposure experienced by these individuals would represent a conservative NOAEL. While there could be human exposure to higher levels of 2,3,7,8-TCDD without producing adverse health effects, the above calculation would, at least, provide conservative estimations of 2,3,7,8-TCDD exposures which would not be of concern.

The biological half-life of 5 years in humans was based on one individual whereas the median value of 7.1 years estimated by CDC (1987b) was based on 36 individuals. Syntex believes that 7.1 years is the best estimate at this time of the biological half-life in humans.

The background of Kimbrough's 1 ppb level of concern should be explained. For example, the level of concern was intended to be only a guideline developed for one set of conditions and not a standard to be applied anywhere 2,3,7,8-TCDD is present in residential soil. In addition, the level of concern is based on such assumptions as: 100% of the soil surface area is contaminated with 2,3,7,8-TCDD; persons will spend their entire 70 year lifetime in the contaminated area; and children who eat an abnormally large volume of dirt will reside in the area of contamination. Reference should be made to the work of Paustenbach _et al_. (1986) who critically evaluated the rationale of Kimbrough's 1 ppb "level of concern" value. CDC itself is currently re-evaluating its 1 ppb level of concern.

2.2.3.2 Human exposure potential

There is no evidence to suggest that the primary route of human exposure is by the dermal route, and unless the ATSDR quantifies the exposure by each route, it should not assume that the dermal route of exposure is the primary route of exposure. While it is true that workers involved in the manufacture of 2,4,5-trichlorophenol and 2,4,5-T received the highest exposures of 2,3,7,8-TCDD (in view of the numerous reported cases of chloracne), the primary route of such exposure may have been by inhalation of dusts and vapors, or by ingestion, due to poor personal hygiene practices. Because the manufacture of 2,4,5-trichlorophenol and 2,4,5-T have been banned, these types of exposures no longer occur. The types of potential exposures that occur today result primarily from environmental sources of 2,3,7,8-TCDD: landfills, fly ash, etc. Dermal exposure from these sources of 2,3,7,8-TCDD would not be expected to be as high. Thus, depending on the source of the 2,3,7,8-TCDD to which people are exposed, the primary route of exposure will be different. The format of the Draft Profile of dividing exposures and toxicities according to route of exposure should be changed since occupational and environmental exposures occur by all routes.

The Draft Profile states in this section that, "Inhalation may be of particular concern where contaminated soils are being excavated or dust is being formed by other activities." Fairless et al. (1987) found 2,3,7,8-TCDD levels in airborne dust between 1 and 1.5 pg/m^3. In comparison, CDC recommends a standard of 5.5 pg/m^3, and EPA recommends a standard of 3 pg/m^3.

Whenever the Draft Profile discusses 2,3,7,8-TCDD exposure in qualitative terms, e.g., "exposure through ingestion of fatty tissues of fish that inhabit contaminated areas is anticipated to be significant" and "elimination of 2,3,7,8-TCDD through mother's milk can result in large exposures to the infant", the qualitative terms can easily be misconstrued to imply that these exposures are hazardous. Because the significance of exposure is dependent upon the concentration of 2,3,7,8-TCDD in the fish or milk, the qualitative phrases should be omitted. As discussed earlier, ATSDR should instead determine acceptable concentrations of 2,3,7,8-TCDD in sources of potential human contact, such as human milk and fish. This paragraph of the Draft Profile discusses the theoretical presence of 2,3,7,8-TCDD in sources of potential human exposure. Dr. Arnold Schecter has recently released information to the press (which has not been peer-reviewed) that he has found 2,3,7,8-TCDD in human milk fat in the U.S. at levels proportional to the levels in fat in other parts of the body. While we are unable to assess the accuracy of this finding, it is not surprising since levels in fat after chronic low level exposure should be in equilibrium. As discussed in our comments on the determination of an appropriate toxicity standard, infant exposure to the levels in human milk reported by Dr. Schecter should not be a cause for concern. The daily dose of 2,3,7,8-TCDD would be well below the level established by a properly calculated toxicity standard for 2,3,7,8-TCDD.

2.3 Adequacy of Database

2.3.1. Introduction

While the Draft Profile recites the need for additional data and research at various points in the profile, the statement at the conclusion of Section 2.3.1 indicates that specific research programs will be developed in the future. Because of the large volume of data that has already been generated concerning 2,3,7,8-TCDD, including the data cited in our comments pertaining to the calculation of a NOAEL in humans, additional research is not needed to develop levels of exposure "that may present significant risk of adverse health effects in humans." (Section 110 (3)(C) of SARA). We therefore suggest that Section 2.3.1 indicate that specific research programs are not needed because sufficient data exists to develop health effects levels for 2,3,7,8-TCDD.

2.3.2.1 Introduction and graphic summary

Fig. 2.5 is misleading in that it appears there are some data in humans for several toxicity endpoints by the dermal route but no data at all by the inhalation or oral routes. ATSDR assumes human exposures occurred primarily by the dermal route without providing adequate quantitative justification. While ATSDR indicates at various points in the Draft Profile that exposure by the inhalation and oral routes occurred concurrently, Fig. 2.5 taken by itself (and many readers will no doubt take Fig. 2.5 by itself as a quick summary) does not reflect the fact that human exposure is a sum of all routes of exposures. We suggest putting a qualifying statement on the same page as Fig. 2.5 or modifying Fig. 2.5 to represent better the existing database. Also, the significance of the asterisks in Fig. 2.5 should be explained.

Throughout the Draft Profile, ATSDR organizes the data as if human exposure occurred primarily by the dermal route and then states the qualification that exposure by the other routes occurred as well. Syntex suggests that the breakdown of human data by route of uptake is unwarranted unless it is known that exposure to 2,3,7,8-TCDD occurred by one route. In general, of course, these data can only come from laboratory experimentation.

2.3.2.2 Descriptions of Highlights of Graphs

In light of the uncertainties of estimating past human exposure and the presence of confounding chemicals, the data of Kligman on prisoners (as cited in Rowe, 1980) should be given serious consideration. The study clearly demonstrates chloracne as the most sensitive indicator of toxicity and provides a dosage range for the NOAEL/LOAEL. The study also provides a conservative value for the LD_0 in humans, since none of the subjects died from their exposure. Comparing this LD_0 to the LD_{50} in animals would provide valuable insight on the issue of the sensitivity of humans as compared to other species.

2.3.2.3 Summary of relevant ongoing research

There are additional research projects currently under way that are not listed in Young and Kang (1985). A more recent article describing several federally funded projects on 2,3,7,8-TCDD is found in Hanson (1987). Syntex suggests that ATSDR list in the form of an appendix at the end of the Draft Profile all ongoing research projects on 2,3,7,8-TCDD (epidemiology, toxicokinetics, mechanism of action) rather than just providing a reference.

2.3.3.1 Pharmacokinetics and mechanisms of action

There are several groups working on the mechanism of action of specific endpoints of 2,3,7,8-TCDD toxicity. ATSDR's discussion of only Rozman's study has the effect of mischaracterizing the totality of research being conducted in this area. A brief discussion of the work by Peterson's and Gasiewicz's groups on the wasting syndrome and gastrointestinal effects (Peterson et al., 1984; Huang-Lu et al., 1987), Birnbaum's work on reproductive effects (Lamb et al., 1986; Abbott et al. (1987), Luster's work on immunological effects (Tucker et al., 1986) and the work of other prominent 2,3,7,8-TCDD researchers should be included.

In light of methods proposed by Gehring (1984) and Commoner et al. (1986) to convert the body burden of 2,3,7,8-TCDD to daily doses, any additional pharmacokinetic work should be directed toward refining these approaches. Body burden data are useful principally as an estimate of past exposure. Knowing what daily dose results in a particular body burden provides a method of comparing human exposure to animal exposure, which is generally in terms of known daily doses. At this point, the only remaining major issue is what safety factor, if any, to use to avoid adverse health effects in humans.

2.3.3.2 Monitoring human biological samples

We agree with the last sentence in this section, which indicates that the ability to monitor 2,3,7,8-TCDD in human tissue appears to exceed the ability to interpret the toxicological significance of the results. Devoting resources to develop more sensitive analytical methods for environmental analysis does not appear fruitful at this time because exposures to these levels (below ppt) will not impact human health.

2.3.3.3 Environmental considerations

The inability to detect 2,3,7,8-TCDD in ambient air and drinking water should not be unduly alarming since exposure and uptake of 2,3,7,8-TCDD in these media at the current limit of detection is so low that any adverse health consequences is de minimus.

The bioavailability of 2,3,7,8-TCDD on soil by the oral and dermal routes of administration was addressed by Shu et al. (in press, a). A major concern is the bioavailability of 2,3,7,8-TCDD from fly ash. This issue has received attention by van den Berg et al. (1983, 1985, 1987).

3. CHEMICAL AND PHYSICAL INFORMATION

3.2 Physical and Chemical Properties

Many of the values in Table 3.2 attributed to Schroy et al. (1985) are estimated values. When multiple values are presented for a given property, e.g., water solubility, the "best estimate" should be indicated. For instance, there is general consensus that the water solubility of 2,3,7,8-TCDD is 19.3 ng/L.

One notable deficiency in Table 3.2 is the inclusion of the value for water solubility of 317 ng/L. A value of 19.3 ng/L (6×10^{-11}M) has been established experimentally and has been independently verified. The value for Henry's constant in Table 3.2 was calculated using the estimated solubility of 317 ng/L and hence, is incorrect. For a correct calculation of Henry's constant, ATSDR should consult Podoll et al. (1986). Podoll et al. (1986) measured the vapor pressure of 2,3,7,8-TCDD at 25°C and recalculated Henry's constant using measured rather than estimated values. Their calculation of Henry's constant is as follows:

$$H = 7.4 \times 10^{-10} \text{ torr}/6 \times 10^{-11} M = 12 \text{ torr-}M^{-1}$$

The statement in this section that decomposition is virtually complete within 21 seconds at 800°C is essentially correct, although it should be recognized that higher temperatures will produce more rapid decomposition. For example, a temperature of 900°C will decompose 2,3,7,8-TCDD is less than 3.0 seconds while a temperature of 1000°C will accomplish this feat in less than 0.2 seconds.

4. TOXICOLOGICAL DATA

4.1 Overview

The toxicity of 2,3,7,8-TCDD has been extensively studied in animals and humans. While it has been shown to produce numerous toxic effects to animals, the only demonstrated toxic effect in humans is chloracne.

Human exposure to 2,3,7,8-TCDD in the past has been highest during the manufacture and use of herbicides and germicides containing trace quantities of 2,3,7,8-TCDD as an impurity. Because these activities have ceased, current potential human exposures to 2,3,7,8-TCDD are lower. Even with higher 2,3,7,8-TCDD exposures in the past, the only demonstrated effect in humans was chloracne. It is therefore unlikely that present levels of human exposure to 2,3,7,8-TCDD are a cause for concern.

The first paragraph of this section states that 2,3,7,8-TCDD is "absorbed well through the skin." Devoid of context, this phrase is uninformative. Shu _et al_. (in press, b) found that about 1% of 2,3,7,8-TCDD adsorbed on soil was absorbed through rat skin after 24 hours. Poiger and Schlatter (1980) reported similar results. Banks-Case _et al_. (1988) reported that dermal absorption of 2,3,7,8-TCDD in acetone decreased with increasing concentrations of 2,3,7,8-TCDD applied to the backs of rats. The highest percentage absorbed was 22% (at the lowest dose tested, 0.1 μmol/kg).

It is generally recognized that 2,3,7,8-TCDD metabolism results in detoxification (as stated in paragraph one). However, other sections of the Draft Profile appear to imply that enzyme induction is an indicator of toxicity (Sec. 2.3.2.2; Sec 4.1). In these sections the use of the phrase "induction of hepatotoxic effects" is confusing because it is not clear whether the Draft Profile considers the "enzyme induction" effect of 2,3,7,8-TCDD to be an hepatotoxic effect. Enzyme induction is considered an adverse effect for chemicals that are biotransformed to more toxic intermediates by these "induced" enzymes. This is not the case with 2,3,7,8-TCDD. The enzymes induced by 2,3,7,8-TCDD actually facilitate the elimination of 2,3,7,8-TCDD and thus should be considered a "protective effect".

By indicating that elimination half-lives vary "from 11 days in the hamster, which is relatively resistant to 2,3,7,8-TCDD toxicity, to more than one year in the monkey, which is sensitive to the toxicity of 2,3,7,8-TCDD", the last sentence in paragraph one could be read as inferring that sensitivity is correlated with elimination half-life. This inference should be removed since the varying sensitivity of different species to the toxicity of 2,3,7,8-TCDD is <u>not</u> correlated with elimination half-life. For example, rats and mice are intermediate in sensitivity to the effects of 2,3,7,8-TCDD, but have elimination half-lives similar to that of guinea pigs, the most sensitive species (Gasiewiz <u>et al</u>., 1983).

In addition, even though the elimination half-life of 2,3,7,8-TCDD in humans is estimated to be greater than 5 years, there is evidence that humans are not very sensitive to the acute toxicity of 2,3,7,8-TCDD, and that in fact humans may be one of the least sensitive species. The data of Kligman (as cited in Rowe, 1980) suggest that the extrapolated LD_{50} of 2,3,7,8-TCDD in humans is in the same range as in rabbits, and may be much greater.

Syntex agrees with the first sentence in paragraph three which states that "The only effect clearly demonstrated to be produced in humans following 2,3,7,8-TCDD exposure is chloracne." However, this conclusion is not clearly stated in Section 1.4, which states that there is "suggestive evidence" that 2,3,7,8-TCDD causes adverse effects on the liver, appetite and weight loss, and digestive disorders. Nor is the point made in Section 2.2.1.2, which states that the four major toxic effects of 2,3,7,8-TCDD are chloracne, wasting syndrome, hepatotoxicity, and immunotoxicity; or in Section 4.1, which states that there is "suggestive evidence" that 2,3,7,8-TCDD affects the nervous system and the liver in humans. There is more than "suggestive evidence" that these effects <u>are not</u> associated with 2,3,7,8-TCDD at the levels of exposure in question. In order to be internally consistent and to accurately reflect the data, Sections 1.4, 2.2.1.2, and 4.1 should emphasize that the adverse effects have not been demonstrated to occur in humans as a result of exposure to 2,3,7,8-TCDD.

The overview of 2,3,7,8-TCDD toxicity should emphasize that chloracne is the most sensitive and the only documented health effect observed in humans (Suskind, 1985). Other effects have been reported in individuals with chloracne, but by reason of concurrent exposure to other agents which cause these other effects, it has not been demonstrated that the adverse health effects were caused by 2,3,7,8-TCDD. As to those effects which have been reported in individuals who do not have chloracne, they undoubtedly were caused by other factors.

Syntex agrees with the conclusion drawn by the Draft Profile that, while immunotoxicity may be one of the most sensitive effects of 2,3,7,8-TCDD in animals, it has yet to be demonstrated to occur in humans. All the studies which evaluated the immune system in humans thus far have been negative. These evaluations include: the studies of Seveso residents (Reggiani, 1980; Sirchia et al., 1982a,b); the Ranch Hand Morbidity and Follow-up studies (Lathrop et al., 1984, 1987); and the follow-up study of Missouri residents (Harmon, 1987; Evans et al., 1987).

While there exist conflicting data on the effect of 2,3,7,8-TCDD on human reproduction, the draft profile should evaluate several additional studies, which indicate that 2,3,7,8-TCDD does not affect human reproductive outcome. These include Stockbauer et. al., (in press), Townsend et al. (1982), Hatch and Stein (1986), Reggiani (1980), and Pitot Committee Report (1986). The weight of the scientific evidence does not support the conclusion that adverse reproductive effects in humans are attributable to 2,3,7,8-TCDD exposure.

The overview of 2,3,7,8-TCDD's genotoxicity should be stated more definitively. While EPA's Health Assessment Document (1985a) concluded that the data were inadequate to assess the genotoxicity of 2,3,7,8-TCDD fully, it is clearly IARC's position that 2,3,7,8-TCDD is not genotoxic (IARC, 1982). Recent reviews of the literature have also concluded that 2,3,7,8-TCDD is not genotoxic (Kociba, 1984; Pitot Committee Report, 1986; Fishbein, 1987; Shu et al., 1987).

The evidence clearly demonstrates that, at the levels of exposure experienced by industrial workers, Vietnam veterans, herbicide sprayers, Seveso residents, and all other exposed groups, no increase in cancer resulting from 2,3,7,8-TCDD exposure has been established (AMA, 1984). The studies that purport to have found an increase in cancer have been properly criticized as flawed and unreliable (Cole, 1980, 1981).

4.2 Toxicokinetics

4.2.1.2 Oral

The percentage of 2,3,7,8-TCDD absorbed by the human body is highly dependent upon the source of exposure. 2,3,7,8-TCDD in corn oil (the source used by the study referenced in the Draft Profile) has significantly greater bioavailability than sources of 2,3,7,8-TCDD to which humans may be exposed, e.g., soil, fly ash. ATSDR should consider the articles by van den Berg et al. (1983, 1985, 1987) and the article by Shu et al. (in press, a) in its evaluation of the oral bioavailability of 2,3,7,8-TCDD. Van den Berg et al. (1983, 1985, 1987) addresses the oral bioavailability of 2,3,7,8-TCDD from fly ash, a matter that the Draft Profile has not addressed.

4.2.1.3 Dermal

The Draft Profile should explain that it is even more difficult to extrapolate dermal absorption data from animals to humans than to extrapolate oral absorption data. In animals, the compound is usually applied occluded to skin for 24 or 48 hours, whereas in humans, the skin is in contact with contaminated materials for only a short time, and is rarely occluded. Physico-chemically, the 2,3,7,8-TCDD adsorbed into soil particulates must first desorb off the particulates, dissolve in oils on the skin surface, and then migrate through the skin. The desorption and dissolution steps suggest a lag phase before initial absorption occurs.

Data from Shu et al. (in press, b) confirmed the data by Poiger and Schlatter (1980) indicating that about 1% of 2,3,7,8-TCDD on contaminated soil is dermally absorbed by rats over a 24 hour contact period. Shu et al. (in press, b) also demonstrated that two parameters contribute to overestimating the dermal absorption of 2,3,7,8-TCDD by humans: (1), dermal absorption following 4 hour contact with soil (which would be typical of a gardener's exposure) is about 60% of that following 24 hour contact (the exposure period used in the animal studies); and (2), human skin is about ten times less permeable to lipid-soluble compounds such as TCDD than is rat or rabbit skin.

4.2.2.2 Oral

While Poiger and Schlatter (1986) reported that 87% of the administered dose was absorbed, they did not assume that all of the absorbed dose resided in adipose tissue, as is incorrectly indicated in the Draft Profile.

Because human body burden is the result of exposure through a combination of ingestion, inhalation, and dermal uptake, Syntex suggests the addition of a Section 4.2.5 on human body burdens which would include a comprehensive review of the literature, including a table showing the levels that have been reported. 2,3,7,8-TCDD levels in adipose tissue and serum lipids should be relied upon as the most definitive indicator of past exposure.

Once 2,3,7,8-TCDD is absorbed into the bloodstream by any route of administration, there is no reason to expect that its distribution would depend on the route of administration.

4.2.3 Metabolism

The implication of paragraph two is that because 2,3,7,8-TCDD metabolites are less toxic than the parent compound, hepatic enzyme induction should be considered a detoxification mechanism in that the 2,3,7,8-TCDD would be more rapidly metabolized. This is the most widely accepted view in the field of drug metabolism and should be reflected in the Draft Profile. Enzyme induction is not considered an adverse effect unless the parent compound is activated to more toxic metabolites, as in case of benzo(a)pyrene, but not in the case of 2,3,7,8-TCDD.

4.2.4 Excretion

CDC (1987b) reported a median elimination half-life of 7.1 years in 36 Vietnam veterans exposed to 2,3,7,8-TCDD. While this compares favorably with the value of 5 years estimated by Poiger and Schlatter (1986) in one individual, the range in CDC (1987b) was 3 to 28 years. Furthermore, the authors reported that the subjects used in this study were not randomly selected. The limitations discussed above should be considered when using the elimination half-life in humans in any pharmacokinetic calculations.

Regarding the last sentence in Section 4.2.4.2, it should be noted that McNulty et al. (1982) and Bowman et al. (1987) both reported an elimination half-life of approximately one year in monkeys. Since ATSDR is responsible for making an independent evaluation of available information, secondary sources such as EPA's 1985 Health Assessment Document should be relied on less than primary literature.

4.3 Toxicity

The format of this section creates difficulties because it is organized by particular routes of exposure. While in animals this is appropriate (since the route of exposure is known), in humans it is inappropriate, since exposure is invariably by all three routes. Because little experimental research is done on humans with 2,3,7,8-TCDD, or with most industrial chemicals, consideration of the adverse health effects in humans according to route of exposure is not practical.

It is inaccurate to state that "no studies are available" to address the issue of 2,3,7,8-TCDD's effects on lethality and decreased longevity in humans. From all the sources of 2,3,7,8-TCDD exposure identified earlier, not one human death has been reported. This is a rather significant finding, especially in light of the popular perceptions of the hazards of 2,3,7,8-TCDD.

4.3.1.3 Dermal

ATSDR should consider the critical dermal toxicity study by Kligman (as cited in Rowe, 1980). In this study, varying doses of 2,3,7,8-TCDD dissolved in a 50:50 mixture of alcohol and chloroform were administered to the foreheads and backs of prisoners to try to determine the chloracnegenic dose. Ten subjects were used at each dose level (total doses of 2,3,7,8-TCDD applied were 0.4, 1.0, 2.0, 4,0, 8.0, 16.0 and 7500 µg). No subjects developed chloracne except at the highest total applied dose (at which eight out of ten subjects developed chloracne). The chloracne disappeared after 4 to 7 months. No other clinical evidence of toxicity was detected from routine physical examination, hematological analysis, or urinalysis. This study indicates that the NOAEL for chloracne in humans lies between 16 and 7500 µg of 2,3,7,8-TCDD (applied dose). While this range is quite large, it nevertheless is of great importance because this study was performed on humans and because chloracne is the most sensitive indicator of 2,3,7,8-TCDD toxicity in humans.

Although the Kligman study is not peer-reviewed, it should receive serious consideration. The Guidelines for Development of Toxicological Profiles, 52 Fed. Reg. 12870 et seq. (April 17, 1987) anticipate that data from studies not yet peer-reviewed will be used in the Profiles. For example, the Guidelines provide that "Toxicity data that are used to support the principal conclusions of a profile and which have not previously been peer reviewed will be subject to an independent peer review consistent with section 110 of SARA."

The prisoner study by Kligman (as cited in Rowe, 1980) can be used to calculate a dose that does not cause death in humans since no fatalities occurred at the highest dose administered. Depending on the value used for dermal absorption of 2,3,7,8-TCDD suspended in solvent, the dose in humans that does not cause death is calculated to be at least 10.7 μg/kg (if 10% bioavailable) or at least 107 μg/kg (if 100% bioavailable). Because this is an LD_0 and because of lower permeabilities in human skin than animal skin, the estimated human LD_{50} would be higher than the administered LD_{50} dose to rabbits of 275 μg/kg. Finally, because human exposure will usually be to 2,3,7,8-TCDD adsorbed to particulates where bioavailability is lower than in solvent, and because exposures typically will be for a few hours only, the dermal LD_{50} of 2,3,7,8-TCDD to humans exposed to environmental sources of 2,3,7,8-TCDD can be expected to be higher still.

Kligman's data can also be used to estimate the acute toxicity of 2,3,7,8-TCDD of humans relative to animals. For instance, assuming 100% bioavailabilty, the LD_{50} in rabbits is 275 μg/kg and the LD_0 in humans is at least 107 μg/kg. The extrapolated LD_{50} in humans is probably in the same range as in rabbits, and may, in fact, be much greater. Certainly the data indicate humans are not as sensitive as some of the more sensitive species tested (whose LD_{50}'s are below 100 μg/kg, albeit by the oral route of administration). The Draft Profile states on page 33, paragraph two, that "rabbits are intermediate in sensitivity to 2,3,7,8-TCDD in oral toxicity studies." Because there is no reason to suspect that the route of exposure affects the behavior of 2,3,7,8-TCDD once absorbed into the body, one can conclude that humans are relatively resistant to the acute toxic effects of 2,3,7,8-TCDD.

4.3.2.1 Chloracne

Under the section addressing dermal exposure in humans, the study by Kligman (as cited in Rowe, 1980) should be discussed. Kligman's results do not contradict any published data on 2,3,7,8-TCDD, and, in fact, corroborate other 2,3,7,8-TCDD toxicity data. If one goes through the exercise of estimating the exposures that have occurred in various human populations, one will find that Kligman's data is in agreement with these estimates.

For example, it has been reported that a woman in Seveso who died from pancreatic cancer seven months after the explosion (cancer that was unrelated to her 2,3,7,8-TCDD exposure) had a body burden of 40 µg (Reggiani, 1981 as cited in Young, 1984). She did not have chloracne. If her body weight was that of a typical adult female of 60 kg, then her dose was approximately 0.67 µg/kg. Her two young nephews, who were reported to have had skin rashes, and possibly chloracne, were most likely more highly exposed. All exposure estimates that have been conducted indicate that children have been more highly exposed to contaminants found in soil due to their higher soil ingestion rates (Kimbrough et al. 1984; Hawley, 1985; Eschenroeder et al., 1986; Paustenbach et al., 1986; EPA, 1987a). Coupled with a lower body weight, these two young children's exposures were probably at least ten-fold higher than that of the woman. The estimated absorbed doses of the woman and the nephews fall between the NOAEL and LOAEL of Kligman's study and thus are consistent with his results.

Kligman's results are also consistent with the Draft Profile's summation that:

> It is known that chloracne appears prior to any other visible effects related to 2,3,7,8-TCDD exposure.

While there have been reports of a wide assortment of symptoms and adverse health effects from exposure to 2,3,7,8-TCDD, large scale studies of these exposed individuals have resulted in negative findings (AMA, 1984; Bond et al., Chemosphere, in press). Syntex suggests that the second paragraph of page 43 of the Draft Profile include this observation.

Because chloracne is considered the most sensitive indicator of human exposure to 2,3,7,8-TCDD, and since body burden levels of 2,3,7,8-TCDD in adipose tissue and serum lipid are reliable indicators of past 2,3,7,8-TCDD exposure, it should be feasible to estimate the maximum level of exposure (as reflected by the body burden) that does not produce chloracne. Rather than saying that there is insufficient exposure data in humans, ATSDR should attempt to estimate exposures of individuals without chloracne and to develop acceptable exposure standards accordingly.

4.3.2.2 Wasting syndrome

Syntex agrees with the final sentence in this section, which states that "no reports of abnormal weight change as a result of 2,3,7,8-TCDD exposure in humans were found." However, Section 4.3.2.1 states that "These signs [from 2,3,7,8-TCDD exposure] include aching muscles, loss of appetite, weight loss, digestive disorders,...". Section 4.3.2.1 should be amended to clearly indicate that the listed health effects have never been demonstrated to result from human exposure to 2,3,7,8-TCDD.

4.3.2.3 Hepatic effects

The Draft Profile does not provide calculations to support its position that human exposure to herbicides and other industrial chemicals contaminated with 2,3,7,8-TCDD occurs primarily by the dermal route. Because of the format of the Draft Profile, there is no appropriate section to discuss most human exposures because they occur by all routes of exposure rather than by a specific route of exposure.

The issue of whether hepatic enzyme induction is an adverse effect has been addressed earlier in Sections 1.4 and 4.2.3. Briefly, if 2,3,7,8-TCDD is detoxified by the induced enzymes, then enzyme induction should be classified as a protective rather than adverse effect.

On the issue of whether enzyme induction is a sensitive indicator of 2,3,7,8-TCDD toxicity, the Kligman study of prisoners also assessed various hematological parameters indicative of liver function. Kligman found these hematological parameters to be normal, even in the group that developed chloracne. Thus, his results would confirm chloracne as the most sensitive indicator of 2,3,7,8-TCDD toxicity.

4.3.2.4 Immunotoxicity

In the first sentence of the paragraph on immunotoxicity to animals by the oral route, Knutsen (1984) is incorrectly cited. Knutsen (1984) deals with immune effects in humans. In the studies by Stehr et al. (1986) and Hoffman et al. (1986), there is no evidence to suggest exposure was primarily by the dermal route such as to warrant discussion of their studies in this section.

Syntex agrees with the Draft Profile's conclusion that in the pilot epidemiologic study of residents in Missouri, Stehr et al. (1986), did not find any signs of immunotoxicity.

The immunotoxicity results of Hoffman et al. (1986) should be discounted because, among other reasons, there were serious flaws in the protocol used and follow-up studies showed no abnormal effects (Harmon 1987; Evans et al., 1987).

It was pointed out in the Pitot Committee Report (1986) that there were flaws in the protocol used in Hoffman et al. (1986). The Pitot Committee Report (1986) stated:

> ...some biases may have been introduced into the study whose impact can not be evaluated as follows: 1) The four regular skin test readers did not read the DTH response of 26 participants and the skin tests for these individuals were read by 12 individuals. Because of the lack of standardized training among these 12 readers, disproportionate mix of exposed and unexposed participants, and potential for knowing subject exposure status these skin test results were excluded from the analysis. 2) The frequency of anergy observed by two of the four regular readers (readers 1 and 2) in unexposed participants was 15% and 40%, respectively, rates significantly higher than expected ($P < .01$) when compared with published norms for a healthy population (0.2%). Skin test results for all participants examined by these two readers were excluded from subsequent analyses of DTH results. Results were therefore reported only for the 145 participants (54% of the total group, accounting for 39% of the exposed group and 68% of the unexposed group) examined by the acceptable readers. 3) There was a statistically significant difference between the exposed and unexposed groups for the mean Hollingshead index score for the head of the household ($p<0.01$) which is inversely related to socioeconomic level, and the participants educational level ($p<0.01$). Educational and socioeconomic levels were lower in the exposed group. Another concern in the above mentioned study is that the multitest CMI assay system used to assess delayed cutaneous reactivity to recall antigens produced less than the expected frequency of reactivity previously reported in normal controls (Kniker et al., 1984). It is presently not clear what if any impact these factors may have had on the Missouri study, and the participants are being evaluated further.

In addition, the clinical significance of the various indicators of cell-mediated immunity reported in Hoffman et al. (1986) is uncertain. For example, in the Manual of Clinical Laboratory Immunology (1986), it states:

> The ratio of CD4 [T4] to CD8 [T8] cells is sometimes used to concisely express the status of the immune system. The validity of this expression is controversial. The major objection is that the CD4 and CD8 subsets are now known to be made up of several diverse and distinct cell populations.

It should be noted that a follow-up study of the population evaluated by Hoffman et al. (1986) has been conducted, and that it showed no abnormal effects (Harmon 1987; Evans et al., 1987). Evans et al. (1987) stated the following:

> In an effort to provide retesting for all participants with reported anergy or relative anergy on initial testing, we performed a follow-up evaluation. Of those participants who were initially unexposed individuals enrolled in the follow-up study. Similar tests to those performed in the initial study were repeated.
>
> The results indicated that the only T-cell measures outside the normal range were the T4% and T4/T8 ratios in the exposed group. The repeat skin test results indicated that none of the participants was anergic and only one exposed and one unexposed participant were relatively anergic. Hematology and physical exam parameters were essentially normal and comparable in exposed and unexposed participants in both studies.
>
> The most important finding of this follow-up study was the failure to confirm depressed DTH skin test reactions in the TCDD-exposed cohort.

The immunological evaluation of the Ranch Hand group was also negative (Lathrop et al., 1984, 1987). The overall conclusion of the immunological status of the Ranch Hand group was stated in Lathrop et al. (1987) as follows:

> Overall, there were no significant group differences or any indication of impaired immunological competence in either group based on comprehensive cell surface marker and functional stimulation studies. Six cell surface markers (total T cells, helper T cells, suppressor T cells, B cells, monocytes, HLA-DR cells, and a constructed helper/suppressor ratio variable) and three functional stimulation studies (PHA, pokeweed, and mixed lymphocyte culture) were conducted on 47 percent of the study population. No significant differences were revealed for five of these variables. In the analyses of the other five variables, there were significant group-by-covariate interactions, but no discernable pattern was identified to

> suggest a detriment in any subgroup of either group. Skin test assessments of delayed hypersensitivity were characterized by inter-reader variation and shifting diagnostic criteria for anergy. The skin test data were judged invalid and were not subjected to statistical testing for group differences. No consistent pattern of immunological deficits could be associated with increasing levels of herbicide exposure in the Ranch Hand group.

Studies of the immunological status of Seveso residents exposed to 2,3,7,8-TCDD revealed little evidence of impairment of the immune system (Reggiani, 1980; Sirchia et al., 1982a,b). While Sirchia et al. did find elevated serum complement, most immunologists would not consider this an abnormal or deleterious finding. The studies of Sirchia et al. (1982a,b) of Seveso children are particularly significant because many of the children in the study had sufficiently high exposure to 2,3,7,8-TCDD to have developed chloracne.

It is true, as noted in the second paragraph of the "General Discussion," that there are little data available regarding dose-response relationships and species and strain differences in sensitivity, and that such data would be of assistance in evaluating response with respect to human health. What is more important, however, is to try to quantify past and future human exposure, duly recognizing that no immune effects were found under past exposure scenarios and that future exposures will tend to be lower than what has occurred in the past. Because exposure to 2,3,7,8-TCDD is decreasing and will continue to decrease, immunotoxicity, as well as other endpoints of toxicity, is even less likely to occur in the future.

results in all assays. McCann's conclusions are in conflict with those of Seiler and Hussain et al. on strain TA1532. However, McCann's results cannot be compared directly with those of Hussain et al. because of differences in study protocol. McCann's studies were performed with both the spot test and the plate incorporation procedure. The plate incorporation procedure is considered the standard procedure today. Hussain used the liquid incubation procedure, a procedure which is no longer routinely used because of higher incidence of false positives. [In the liquid incubation procedure, the test substance and bacterial cells are incubated in liquid suspension and subsequently plated on selective plates. "Artifactually positive responses frequently are reported by investigators who (in the Salmonella/Ames/microsome assay) fail to control the carry over of histidine into the selective plate . . .") (National Research Council, 1983).] McCann's data show that TCDD was not active in the presence or absence of metabolic activation in 3 strains which test for frameshift mutations and in 1 strain which tests for base-pair substitution.

4.3.6 Carcinogenicity

4.3.6.3 Dermal

As discussed above, there is no evidence to indicate that human exposure occurred primarily by the dermal route.

A brief review of the carcinogenicity of the compounds to which one is exposed concurrently with 2,3,7,8-TCDD would be useful. For instance, if 2,4-D or 2,4,5-T are potent carcinogens themselves, then the issue of whether 2,3,7,8-TCDD is a human carcinogen is even more problematical.

As with all the other toxicity studies, the merit of each epidemiology study requires critical evaluation. The studies by Hardell and co-workers purporting to show increased incidences of soft tissue sarcomas and lymphomas among herbicide sprayers have been criticized for methodological flaws. For instance, testimony presented before the EPA in 1980 and 1981 by Dr. Philip Cole, Professor and Head, Division of Epidemiology, School of Public Health, University of Alabama, which is available to the general public, raises serious questions concerning the methods used and conclusions drawn by Hardell and coworkers and others. As stated in Cole (1980):

> My testimony describes general methodologic issues in case-control and retrospective follow-up studies of cancer and evaluates the epidemiologic studies pertinent to the possible carcinogenicity of 2,3,7,8-tetrachloro- dibenzodioxin (TCDD) and of phenoxy acid herbicides, especially formulations which contain TCDD. My evaluations are based on the original papers and on additional information both from the direct and cross-examination testimonies of previous witnesses in this hearing.
>
> The case-control study design is the most valuable available to the cancer epidemiologist. However, such studies must be done with extreme caution and concern for detail.
>
> The three case-control studies by Dr. Hardell and his associates are nearly identical in design. The studies contain many limitations, the most serious of which are the likelihoods of observer and recall bias. Because of these and other problems detailed in my testimony, I consider these case-control studies uninformative with respect to the possible carcinogenicity to human beings of exposure to preparations containing TCDD.
>
> The retrospective follow-up study has the advantage over the case-control study of permitting observation of many different disease outcomes. It is limited, however, because of the difficulties in adequately documenting exposure and deaths that

4.3.3 Developmental Toxicity

4.3.3.3 Dermal

There is no evidence that human exposure was predominantly by the dermal route. Herbicide sprayers or workers occupationally exposed may have worn protective clothing and gloves and not respirators. Exposure may have been primarily by inhalation. Ingestion of soil contaminated with 2,3,7,8-TCDD may have been the major route of uptake in individuals from nearby residences (Kimbrough et al., 1984; Hawley, 1985; Eschenroeder et al., 1986; Paustenbach et al., 1986; EPA, 1987a). As previously noted, the format of the Draft Profile is not appropriate for adequate categorization of human exposure routes.

4.3.3.4 General Discussion

It is not apparent how additional research in the guinea pig and monkey will help answer the question whether 2,3,7,8-TCDD is a developmental toxicant in humans. In any event, we submit that ATSDR should suggest how such information could be helpful. It is possible to collect toxicity data in all species and still learn little about the toxicity in humans.

4.3.4 Reproductive Toxicity

Syntex agrees with the Draft Profile's overall conclusion that past exposures to 2,3,7,8-TCDD have not demonstrated adverse reproductive effects in humans. In addition to the studies cited in this section, there are several additional studies which also support this conclusion.

Stockbauer _et al_. (Am. J. Epidemiol., in press) found no evidence of impairment in reproductive outcome of mothers with potential exposure to 2,3,7,8-TCDD in Missouri. Townsend _et al_. (1982) reported no statistical association between Dow Chemical Company employees exposed to 2,3,7,8-TCDD and adverse pregnancy outcomes of their wives. In the study, they stated the following:

> To determine whether paternal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) or other polychlorinated dioxins might be associated with adverse pregnancy outcomes, an interviewer-administered questionnaire survey was conducted among wives of Dow Michigan Division employees in the Midland, Michigan, area who had been potentially exposed to dioxins. A control group consisted of wives of employees who had no dioxin exposure and whose hire dates were comparable to those of the men in the exposed group. A total of 737 conceptions, which resulted in 637 live births and 100 stillbirths and spontaneous abortions, were identified as having paternal exposure; 2031 conceptions, resulting in 1785 live births and 246 stillbirths and spontaneous abortions, were identified as having no paternal exposure to any isomer of dioxin. Odds ratios were calculated for dependent variables consisting of spontaneous abortions, stillbirths, infant deaths and several categories of congenital malformations. Trend analysis was performed for duration-of-paternal-exposure of 12 months or less, or more than 12 months. Overall, no statistically significant associations were found between any exposure and pregnancy outcome, either before or after stratification by pertinent sets of up to nine covariables.

Hatch and Stein (1986) evaluated the data from 3 major studies for the risk to reproduction attributable to Agent Orange exposure. These studies included the Australian study of birth defects and father's Vietnam service involving 8000 cases and 8000 controls, the CDC study of birth defects and Vietnam service involving 4800 cases and 3000 controls, and the Air Force study of reproductive morbidity in Ranch Handers involving 1200 cases. The data were assessed by the epidemiological criteria of: time-order, probability, strength of association, specificity, consistency and coherence. Although the authors pointed out epidemiological problems associated with these studies, the problems they cited are endemic to any epidemiological study. These problems notwithstanding, the authors' conclusions are worth noting: 1) "service in Vietnam did not . . . raise the risk for fathering malformed offspring", and 2) "for the majority of those potentially exposed, there was not a very large increase in risk, or even a moderate increase, for malformations in general."

Reggiani (1980) has summarized the effect of 2,3,7,8-TCDD on human reproduction in Seveso, Italy. He concluded that no obvious effects on reproduction were noted. This was also the conclusion reached by the Pitot Committee Report (1986).

The three generation reproductive toxicity study in rats by Murray <u>et al</u>. (1979) has resulted in the lowest NOAEL in animals and is typically used in establishing acceptable daily doses for

2,3,7,8-TCDD. However, the Draft Profile proposes a "minimal risk for effects other than cancer" that is apparently based on Nisbet and Paxton's statistical reanalysis of Murray et al. To arrive at the minimal risk level, it appears that a safety factor of 1000 was applied to the LOAEL of 1 ng/kg/day as determined by Nisbet and Paxton (1982). The statistical reanalysis by Nisbet and Paxton is not universally accepted because of flaws in the assumptions that they used. One major flaw is that they considered the effect of 2,3,7,8-TCDD on each animal in the three generation study to be "independent" of one another. As pointed out by Kimbrough et al. (1984), this is not true for compounds such as 2,3,7,8-TCDD. Kimbrough et al. (1984) and the Ontario Ministry of the Environment (OME, 1985), among others, concluded that the LOAEL for reproductive toxicity in the study by Murray et al. (1979) is 10 ng/kg/day and that the NOAEL is 1 ng/kg/day, in concordance with the conclusion by the authors of the study. The Draft Profile should discard the Nisbet and Paxton reanalysis and use the LOAEL and NOAEL developed by Murray et al.

4.3.5 Genotoxicity

It is not surprising to find studies that are both positive and negative for a chemical agent, especially when as many tests by so many different researchers are performed as in the case of 2,3,7,8-TCDD. Each study should be evaluated separately for technical merit, and those studies that have been properly conducted should then be evaluated collectively. This is true of not only genotoxicity studies but also all types of toxicity studies. Certainly, there is overwhelming evidence that 2,3,7,8-TCDD is not genotoxic. The International Agency for Research on Cancer (IARC), based on its review of the literature, has classified 2,3,7,8-TCDD as not being mutagenic (IARC, 1982).The scientific community has reached a consensus that 2,3,7,8-TCDD is non-genotoxic (Kociba, 1984; Pitot Committee Report, 1986; Fishbein, 1987; Shu et al., 1987).

The positive studies of Hussain et al. (1972) and Seiler (1973) are flawed and should not be mentioned. At the least, they should be discounted. Shu et al. (1987) stated the following regarding these studies:

> ...there is good scientific reason to question the conclusions of Hussain et al. and Seiler. These two early positive studies were not consistent in demonstrating a dose-response relationship; nor were the results reproducible by later studies. Moreover, the TCDD concentration used in these studies was greatly in excess of TCDD solubility in water, and the bacterial survival rates were extremely low. By current standards, the results of these studies would not be regarded as demonstrating a positive mutagenesis response (Jackson and Pertel, 1986).
>
> Hussain et al. (1972) tested E. Coli Sd-4 for reversion to streptomycin independence and reported a high mutation frequency (approximately 100 fold control) at a TCDD concentration of about 2 μg/ml, where bacterial survival was 11-18%. At 1 μg/ml TCDD, where bacterial survival was 90%, no increase in mutation frequency over control was observed. A dose response was not demonstrated. Hussain et al. (1972) also tested Salmonella/Ames strains TA1530 and TA1532. They did not observe an increase in mutation frequency in strain TA1530. While they

reported an increased mutation frequency in Salmonella/Ames strain TA1532 (a strain which detects reversion to histidine prototrophy by frameshift mutations) at TCDD concentrations over 2-3 μg/ml and bacterial survival below 50%, no mutagenic activity was observed in either strain at TCDD concentration below 2-3 μg/ml. By structural analogy with acridine and the well documented response of Salmonella/Ames strain TA1532 to frameshift mutagens, Hussain et al. concluded that TCDD acted in strain TA1532 by intercalation into the DNA.

In order to interpret the data by Hussain et al., two facts must be appreciated. First, TCDD solubility in water is approximately 10-20 pg/ml (Marple et al. 1986). Thus only about .000001 of the 1-3 μg/ml TCDD used in the study of Hussain et al. was in solution. It is difficult to explain why Hussain et al. observed mutation frequency comparable to the background rate at 1 μg/ml but significantly increased at 2-3 μg/ml, when both solutions had TCDD in excess of its solubility. Also, the mutagenic effects reported by Hussain et al. occurred at very low bacterial survival rates. For the E. Coli Sd-4 test, bacterial survival was 11-18%; for the strain TA1532 test, it was less than 50%. By current standards, these two complications seriously detract from a definitive conclusion of their findings (Jackson and Pertel, 1986). As we shall discuss, many subsequent studies on the same Salmonella/Ames strain (TA1532) have not reproduced the mutagenic effects reported by Hussain et al.

Seiler (1973) studied TCDD in a number of Salmonella/Ames strains including those which require base-pair substitutions (strains G46, TA1530, TA1531) and by frameshifts (strains TA1531, TA1532, TA1534) to be scored as mutations. Seiler reported that the data indicated TCDD to be a strong mutagen in strains TA1532, a non-mutagen in strain G46 and TA1530, and ambiguous in strains TA1531 and TA1534. Seiler used the spot test, wherein crystals of TCDD are placed in the middle of the agar and bacteria are homogeneously dispersed throughout the agar. In order for the bacteria distal to the crystal to be exposed to TCDD, the TCDD must diffuse from the point source. Given TCDD's limited solubility in water of 10-20 pg/ml (Marple et al., 1986), it is unlikely that significant amounts of TCDD migrated from the point source. McCann (cited by Wassom et al., 1977) subsequently repeated the spot test with TCDD and observed no mutagenic activity.

McCann (cited by Wassom et al., 1977) tested TCDD in Salmonella/Ames strains which act by frameshift (TA1532, TA1537, TA1538) and by base-pair substitution (TA1535) in the presence and absence of metabolic activation. McCann obtained negative

> may have occurred many years in the past. Often, an available cohort of exposed persons is too small to permit valid assessment of the cancer experience associated with exposure to the agent under study.
>
> I have reviewed five retrospective follow-up studies relevant to the evaluation of the carcinogenicity of TCDD-containing products. Two of the studies, by Axelson and Frentzel-Beyme, have been interpreted as positive by their authors. However, both studies are small and have a number of serious limitations. Each is uninformative.
>
> The authors of the other three studies, Zack and Suskind, Cook, et al., and Ott et al., interpret their studies as negative. The results of any one of these studies is of limited value because of its small size. However, in the aggregate, these three well-done studies contribute useful information. They argue persuasively that, over an average follow-up of nearly 19 years, even heavy exposure to TCDD-containing substances does not increase the overall cancer mortality rate.

Furthermore, the extent of human exposure to 2,3,7,8-TCDD is not well documented; Hardell himself has reported no differences in the 2,3,7,8-TCDD adipose tissue levels between the cases and the controls (Hardell et al., 1985).

In addition to the negative epidemiological studies cited in the Draft Profile, the following recent studies were also negative:

- A Center for Disease Control (CDC) study comparing the mortality of 9000 Vietnam veterans with about 9000 non-Vietnam veterans. The 17% higher mortality in the Vietnam veterans were attributed to motor vehicle accidents, suicide, homicide, accidental poisonings, and drug related deaths. No other cause (such as cancer) was identified (CDC, 1987a).

- A study of Air Force personnel (Ranch Handers) reported no significant effects attributed to 2,3,7,8-TCDD exposure (Lathrop et al., 1983; 1984). A follow-up study reported similar conclusions (Lathrop et al., 1987).

- A Veterans Administration study of Vietnam veterans concluded that there was no significant increase in soft tissue sarcomas associated with military service in Vietnam (Kang et al., 1986).

- Dow Chemical Company's studies on mortality rates of chemical plant workers concluded that there was no significant increase in mortality by any cause, including cancer, within this group (Sobel et al., 1985; Cook et. al., Chemosphere, in press; Bond et al., Chemosphere, in press).

- A study by Wiklund and Holm (1986) reported that the risk of soft tissue sarcoma among 354,620 Swedish phenoxy acid herbicide users was not increased.

- A study by the Australian government regarding claims of adverse health effects by the Vietnam Veterans' Association of Australia concluded that these veterans "were not exposed to toxic levels of chemicals in Vietnam; that they are not at any increased risk of fathering children with birth defects, or contracting cancer" (Hall, 1986).

Thus, the preponderance of scientific evidence does not demonstrate that 2,3,7,8-TCDD exposure causes cancer in humans. The very small proportion of the human studies that purport to have found otherwise are flawed and unreliable.

5. MANUFACTURE, IMPORT, USE, AND DISPOSAL

5.1 Overview

Because the manufacture of 2,4,5-trichlorophenol has ceased, the second sentence in the Overview should be stated in the past tense.

Syntex agrees that incineration at high temperatures is a promising method for the destruction of 2,3,7,8-TCDD. Thermal treatment or incineration has a proven track record in destroying 2,3,7,8-TCDD and has in fact exceeded a destruction and removal efficiency (DRE) of 99.9999%. In the vapor phase, this DRE is achieved in less than 2 seconds at 2200 degrees Farenheit. Therefore, the prime responsibility of a thermal treatment system is to evaporate 2,3,7,8-TCDD absorbed onto soils or dispersed in liquids. Once in the vapor phase, complete destruction is easily achieved at the proper temperatures. At the present time, this technology is the predominant remedial technique for rendering 2,3,7,8-TCDD contaminated wastes non-hazardous. This technology also has the advantage over many other disposal methods because other potentially hazardous organic materials in a mixture of wastes are also destroyed simultaneously.

There are several stabilization techniques that should be mentioned besides _in situ_ addition of cementitious and asphaltic materials, including isolation through the construction of an erosion-resistant cap and soil inversion via deep tillage techniques.

5.5 Disposal

The term "disposal" should be used only when 2,3,7,8-TCDD has not been chemically destroyed. Otherwise, the term "destruction" would be more appropriate.

5.6 Stabilization (Proposed)

We suggest the inclusion of a section dealing with 2,3,7,8-TCDD stabilization techniques and propose the following language for your consideration:

> In areas having 2,3,7,8-TCDD - contaminated soils, stabilization may be a more appropriate and cost effective remedy than destruction. 2,3,7,8-TCDD has been shown to be relatively insoluble in water and to bind tightly to soil particles. Investigations conducted by the U.S. Environmental Protection Agency at Missouri sites contaminated by 2,3,7,8-TCDD containing oil have shown vertical migration to be limited to a few inches. Correspondingly, the mobility of 2,3,7,8-TCDD in a soil contamination setting is essentially a function of the mobility of the soil particles. Stabilization measures which both prevent air and water erosion of the soil and preclude physical contact essentially eliminate pathways of exposure.
>
> Solidification involves the addition of cementitious or asphaltic materials to the soil to produce a more coherent, less erosive substance. This is typically accomplished by discing of the soil, addition and mixing of the stabilization agent, and subsequent recompaction.

Isolation involves separation of the contaminated material from the ground surface and, hence, from erosive agents. This physical separation also precludes the possibility of physical contact. Isolation may be accomplished by either placement of a protective layer over the contaminated material, or inversion of the soil horizon to effectively bury the contaminated surficial material. The protective layer may consist of compacted soil with vegetative cover, asphalt or concrete. Soil inversion techniques are well established in the vegetable industry for burial of surficial bacteria and fungi. These techniques are directly applicable to contaminated-soil settings and can be accomplished at low cost with minimal dusting, and can effect 100% burial of the contaminated material.

6. ENVIRONMENTAL FATE

6.2 Releases to the Environment

6.2.1 Production and Use of Certain Herbicides and Chlorophenols

The manufacture and use of 2,4,5-T and hexachlorophene have been banned and its contribution to releases in the environment should be stated in the <u>past tense</u>.

6.2.3 Thermal Reactions

Because the temperature at which incinerators operate is very critical to the efficiency of 2,3,7,8-TCDD destruction, the first sentence in this section should be qualified by stating that, "small amounts of 2,3,7,8-TCDD have been detected in the flue gases from municipal incinerators <u>which are operated at relatively low</u>

temperatures." Typically, municipal and industrial incinerators operate between 500-800°C, whereas incinerators designed to destroy 2,3,7,8-TCDD operate at 980-1200°C.

6.3 Environmental Fate

We take issue with several statements made in this section. First, the Draft Profile states that, "In air, 2,3,7,8-TCDD is likely to be present predominantly in the gas phase." The Draft Profile should identify the source(s) for this statement. We believe 2,3,7,8-TCDD in air is present predominantly adsorbed onto particulates (soil, fly ash, etc.). Second, the Draft Profile states that, "the two processes that may be important for the removal of 2,3,7,8-TCDD [in water] are volatility and photodegradation." We believe 2,3,7,8-TCDD metabolism by microbial organisms (in sediment) and higher species (higher 2,3,7,8-TCDD concentrations present due to bioconcentration) can also play an important role. Third, the Draft Profile speculates that 2,3,7,8-TCDD can leach through soil as a result of solvation with organic solvent or biotic mixing. The solubilization by organic solvents can take place only when the organic solvents are the major constituents of the liquid phase. This is an extremely rare occurrence and one which is quickly reversed by dilution with groundwater. There can be significant migration of 2,3,7,8-TCDD only when the volume of organic solvent is large enough to overcome dilution by groundwater. Fourth, the environmental half-life of

2,3,7,8-TCDD is highly dependent upon the soil characteristics, the mode by which soil was contaminated with 2,3,7,8-TCDD, and climatological conditions. (Kearney et al., 1972; Neal and Beall, 1980; diDomenico et al., 1982; Young, 1983; Palausky et al., 1985). Fifth, the Draft Profile cites several studies which found uptake of 2,3,7,8-TCDD by plants. For a more balanced presentation, the Draft Profile should also present the studies that did not find 2,3,7,8-TCDD uptake by plants (Isensee and Jones, 1971; Wipf and Schmid, 1983).

7. POTENTIAL FOR HUMAN EXPOSURE

7.2.1 Air

Rather than reporting 2,3,7,8-TCDD levels in flue gases, ATSDR should estimate the ambient air concentration of 2,3,7,8-TCDD at potential receptor sites in the vicinity of emission sources (see EPA's draft exposure assessment document, 1987). Then, by using tables listing respiration rates and the best estimate for bioavailability, calculations of daily uptake rates for these receptors could be derived. The values could then be compared with daily uptake rates of other pathways of exposure to give the relative magnitudes of exposure by the various routes. Simply presenting data on air levels is not very informative. If the above calculations are performed, however, they would show in all likelihood that exposure to 2,3,7,8-TCDD by inhalation is minuscule and that the associated risks are de minimus.

7.2.2 Water

2,3,7,8-TCDD has not been detected in drinking water. Relevant additional issues are: (1) the level of human exposure from drinking water, (2) how does that level compare with exposure levels from other routes; and (3) is that level of exposure safe? By using the limit of detection in water and the best estimate for bioavailability of 2,3,7,8-TCDD in water, the first two questions can be answered on a worst case basis. If the appropriate calculations are performed, they would show that exposure to 2,3,7,8-TCDD from water ingestion is minuscule and that the associated risks are de minimus.

Where there are landfills and industrial effluents contaminated with 2,3,7,8-TCDD, the relevant issue are: (1) whether these potential sources of 2,3,7,8-TCDD could get to human receptors; (2) at what levels; and (3) whether these levels are safe? If exposures from these sources are inconsequential compared to exposures from other sources, then resources should not be wasted trying to minimize exposures to these sources. Des Rosiers (1987) reported that the mobility of 2,3,7,8-TCDD applied in waste oil in the environment is, at most, a few centimeters per year.

7.2.4 Other

If 2,3,7,8-TCDD is found in human milk and foodstuffs, estimations of exposure and uptake by potential receptors (analogous to the situation of 2,3,7,8-TCDD in air, water, and soil) should be undertaken.

While adipose tissue is the chief contributor to the body burden of 2,3,7,8-TCDD, this does not mean that blood is a poor indicator of the 2,3,7,8-TCDD body burden (as stated in paragraph three). If a relationship, e.g., the partition ratio, can be established between adipose tissue and blood, then the 2,3,7,8-TCDD level in blood can certainly be used as a reliable indicator of the 2,3,7,8-TCDD body burden. This relationship has been reported by Patterson et. al. (1987).

While human body burden data of 2,3,7,8-TCDD are a useful indicator of past 2,3,7,8-TCDD exposure, they do not indicate future exposure. Consequently, human daily uptake of 2,3,7,8-TCDD by the various routes of exposure still should be evaluated. By using the body burdens found in humans, one can validate the reliability of the pathway exposure assessments. Once validated, the body burdens in humans from future exposures to 2,3,7,8-TCDD contaminated media can be estimated. Commoner et al. (1986) estimated that uptake of

2,3,7,8-TCDD at a rate of 1 pg/kg/day results in a body burden of 10 ppt. Gehring (1984) has also proposed an approach to estimate daily uptake rates from body burden data. Ono et al. (1986) and Travis and Hattemer-Frey (Chemosphere, in press) have estimated that uptake of 2,3,7,8-TCDD from foods of adults living in industrialized countries to be 1 and 0.7 pg/kg/day, respectively.

Once the human daily uptake of 2,3,7,8-TCDD contaminated media is estimated from the body burden data, this human daily uptake can be compared to the daily doses given to experimental animals to determine the margin of safety. This could facilitate the task of regulatory agencies to determine an acceptable safety factor, if any, which is reasonably necessary to protect humans against adverse effects observed in animals. Thus, it is now feasible and appropriate to address the issue of estimating human exposure to 2,3,7,8-TCDD.

7.3 Occupational Exposures

Occupational exposure to 2,3,7,8-TCDD during the production and use of hexachlorophene, trichlorophenol, and herbicides containing 2,4,5-T no longer occurs, since the use of these chemicals has been banned. The principal evidence that occupational exposure to 2,3,7,8-TCDD was significantly higher than that which occurred to Vietnam veterans, Missouri residents, and herbicide sprayers is that some occupational workers developed chloracne while none of the individuals in these other groups developed chloracne.

7.4 Populations at High Risk

This section is inappropriately labeled because it is very likely that these exposures carry with them no increase in risk, let alone "high risk." Since non-genotoxic agents, including tumor promoters, possess a threshold level below which no adverse effects occur, the levels of exposure incurred by these groups would not result in any additional risk if these exposures are still below the threshold. Thus, without quantifying exposure, it cannot be assumed that these populations are at a higher risk, not to mention high risk.

9. REGULATORY AND ADVISORY STATUS

This section should include ATSDR's assessment of the regulations and advisories. Clearly, there are discrepancies among existing standards. Syntex urges ATSDR to develop its own health-based standards rather than rely upon the overly conservative standards cited in this section.

9.2.3 Data Analysis

The VSDs reported by ATSDR for EPA, CDC, and FDA of 6.4, 27.6 and 57.2 fg/kg/day, respectively, are misleading. The Draft Profile should explain that CDC reports a range of 28 to 1428 fg/kg/day, depending on whether liver or other tissues are used in the risk assessment. CDC functionally uses a value of 636 fg/kg/day for recommending standards, such as the 1 ppb level of concern for 2,3,7,8-TCDD in residential soil referenced in section 2.2.3.1 of the Draft Profile. In addition, the FDA has also set a fish advisory of 25 ppt which corresponds to a daily dose of 13,000 fg/kg/day.

ATSDR should also cite the full range of VSDs, including those established by non-U.S. regulatory agencies. It should be noted that the VSDs range from 6 to 13,000 fg/kg/day, with non-U.S. regulatory agencies clustered between 4,000 to 13,000 fg/kg/day. EPA is reviewing its VSD, and an internal Agency committee has recommended a revision of the VSD from 6 to 100 fg/kg/day. Even with this revision, EPA would remain at the conservative extreme in its estimate of 2,3,7,8-TCDD cancer risk.

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